Turk J Gastroenterol *2016; 27: 149-55*

A rapid test for assessing disease activity in ulcerative colitis

COLON

Mihaela Dranga[1,2], Catalina Mihai[1,2], Vasile Drug[1,2], Gabriela Dumitrescu[1], Cristina Cijevschi Prelipcean[1,2]

[1]University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania
[2]Institute of Gastroenterology and Hepatology, Iasi, Romania

Original Article

ABSTRACT

Background/Aims: Direct assessment by endoscopic examination has become a "gold standard" in monitoring patients with ulcerative colitis. However, it is an invasive method, with risks and discomfort for the patients. The aim is therefore to identify a less invasive method of assessing ulcerative colitis activity compared to colonoscopy.

Materials and Methods: A prospective study was conducted among 103 patients with ulcerative colitis. Calprotectin was measured by a semi-quantitative rapid test. For each patient, a complete blood count was performed; liver and kidney functions, glycaemia, serum proteins, and inflammatory markers were also evaluated.

Results: The Mayo score showed direct correlations with fecal calprotectin, C-reactive protein, and the erythrocyte sedimentation rate ($p<0.05$) and indirect correlations with hemoglobin ($p=0.139$). The sensitivity and specificity of calprotectin were 98.0% and 76.7%, respectively. Subsequently, combined analysis of the markers' sensitivity/specificity was conducted.

Conclusion: The semi-quantitative rapid test proved to be a good predictor for differentiating the endoscopic active disease from the inactive one. The individual use of fecal calprotectin presents the highest sensitivity in determining the endoscopic activity. Nevertheless, in monitoring patients, combined determination of the three inflammatory markers studied [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), calprotectin] is more useful in reducing unnecessary colonoscopies.

Keywords: Fecal calprotectin, c-reactive protein, erythrocyte sedimentation rate, hemoglobin, ulcerative colitis

INTRODUCTION

Although the etiology of ulcerative colitis (UC) remains largely unknown, the condition appears to be related to a combination of genetic and environmental factors. The homeostasis of the intestinal mucosa is affected due to a genetically determined alteration of the relationship between the commensal flora and the gut immune system. The central components of the inflammatory pathway seem to be the cytokines. No factor has yet been identified as the initial trigger (1). In recent years, with the advent of biological agents, the goal of treatment has turned from the induction and maintenance of clinical and biological remission to obtaining remission without steroids, decreasing prolonged hospitalization, and surgery leading up to mucosal healing (2).

To achieve these aims, patients require frequent monitoring to estimate the effectiveness of the treatment, the illness severity, and the risk of possible complications. Direct assessment by endoscopic examination has become the "gold standard" for achieving these objectives. This method is nevertheless invasive, risky, and discomforting for the patient as well as costly and time-consuming for the clinician (3).

This context has entailed the need to find surrogate noninvasive markers for the estimation of the endoscopic activity.

C-reactive protein (CRP) is a pentameric protein composed of five monomers and is one of the most important acute phase human proteins. Under normal

Address for Correspondence: Mihaela Dranga E-mail: mihaela_dra@yahoo.com
Received: October 13, 2015 **Accepted:** January 20, 2016

conditions, CRP is produced by hepatocytes in small amounts (1 mg/L). However, following an acute phase stimulus such as inflammation, the production of CRP increases rapidly in the hepatocytes under the influence of interleukin (IL)-6, the tumor necrosis factor (TNF-a), and IL-1b (4). Solem et al. (5) identified significant correlations between CRP and the clinical, endoscopic, and histological activity of the inflammatory bowel diseases (IBDs). A high CRP level is mainly determined by the precipitating cause (in our case, by the activity of the disease), and its half-life is constant for approximately 18 h. Despite these characteristics, there is heterogeneity in the CRP response between Crohn's disease (CD) and ulcerative colitis (UC). CD presents a strong CRP response, whereas the CRP response in UC is modest to absent (6).

The erythrocyte sedimentation rate (ESR) is an indirect marker of acute phase plasma protein concentration. However, it lacks high accuracy as it is influenced by both the morphology and the number of erythrocytes and by other plasma components, such as immunoglobulin (7). Given the large variation in the concentration of plasma proteins in patients with IBDs and the long half-life, ESR does not reflect the clinical condition; the decrease in ESR can take several days, even if there is a rapid and proven clinical improvement (8). Therefore, ESR only roughly assesses the disease activity. In UC, where there is a better correlation between the clinical, endoscopic, and histological scores of the disease activity, the activity is well-correlated with ESR. However, ESR can be normal in the mild forms of the disease (9).

Hemoglobin (Hb) is one of the parameters that are the most frequently used in monitoring IBDs. Its low values are common and are determined both by disease activity and the acute or chronic loss of blood or administered therapy (10).

Calprotectin is an enterodimer present in the cytoplasm of the neutrophils. It is composed of two calcium-binding proteins (S100A8 and S100A9) and constitutes approximately 60% of the cytosoluble proteins of the neutrophils. Under these conditions, calprotectin is a marker of neutrophil influx in the colon and thus, indirectly, a marker of intestinal inflammation (11).

The aim of the present study was to determine the usefulness of the semi-quantitative rapid test Cal Detect ® (Sofar; Florence, Italy) for the determination of fecal calprotectin in predicting endoscopic activity in UC and to identify a less invasive method of assessing UC activity compared to colonoscopy using fecal calprotectin, CRP, ESR, and Hb.

MATERIALS AND METHODS

A prospective study was conducted among 103 patients with evaluated UC in the Institute of Gastroenterology and Hepatology, "Sf. Spiridon" Hospital Iaşi between October 2011 and April 2013.

A worksheet was compiled for each patient; it included personal data (name, age, sex, residence), personal and family history, symptoms and signs of disease, clinical data established by objective clinical examination, complete laboratory tests (complete blood count; glucose; total proteins and albumin; electrolytes; kidney tests: urea and creatinine; liver tests: alkaline phosphatase, alanine amino transferase, aspartate amino transferase, and bilirubin). The patients with comorbidities that could influence the studied parameters (malignancies, infections, chronic and acute liver diseases, kidney diseases, and other autoimmune diseases) were excluded from the study. Furthermore, the inflammatory markers were collected, and fecal calprotectin was dosed by the semi-quantitative rapid test Cal Detect® (SOFAR; Florence, Italy) during the same day but before starting the preparation for colonoscopy.

The diagnosis, the location of the lesions, and the endoscopic activity were determined by endoscopic examination and confirmed by histopathology. Disease activity was classified using the endoscopic Mayo score: remission: 0 or 1, activity>1.

Fecal calprotectin dosage by the semi-quantitative rapid test Cal Detect®

Sampling was performed according to the manufacturer's instructions. The fecal sample was collected with a pallet from the adhesive sheet included in the collection kit. The collection pallet was then inserted in the dilution tube, the cap closed, and then it was well shaken. The tip of the tube was broken and the sample was pipetted onto a special circular hole in the pill. If the test was valid, the control line appeared immediately. The results were read after 2-3 minutes. The first band occurs for a calprotectin concentration of under 15 µg/g and indicates the absence of inflammation. The second band appears at a calprotectin concentration ranging between 15 µg/g and 60 µg/g in the presence of acute inflammation. The appearance of the third band indicates a calprotectin value higher than 60 µg/g, and a high degree of mucosal inflammation.

Ethical considerations

The protocol was approved by the local ethics committee. All participants signed an informed consent.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS; IBM, New York, USA) 18.0 for the prospective analyses, without adjustment for multiple testing, and with nominal significance defined as $p<0.05$.

The continuous variables were described using the ANOVA test.

The relations between the laboratory markers and the Mayo score are reported by Pearson correlation coefficients.

The receiver operating characteristic (ROC) curves were analyzed to assess the optimal cut-off values of the markers. The sensitivity, specificity, and positive and negative predictive values were calculated in 95% confidence intervals for this cut-off value.

RESULTS

The study enrolled 103 patients with UC. The gender distribution showed a preponderance of male cases (68.9%), with a sex ratio M/F of 2.2 / 1.

The patients' age ranged from 20 to 75 years, with a mean of 46.32±14.0 years, and was significantly lower in women than in men (42.13 vs. 48.21 years, p=0.041). The age distribution was consistent between the sexes (p=0.074). Over 70% of patients were from urban areas. The characteristics of the patients are illustrated in Table 1.

Table 1. Patients characteristics

Parameter	Mean value/percentage
Age	46.32±14.0
Sex	
Male	71 (68.9%)
Female	32 (31.1%)
Area of provenience	
Urban	73 (70.9%)
Rural	30 (29.1%)
Disease extension	
Proctitis	16 (15.5%)
Left colitis	56 (54.4%)
Pancolitis	31 (30.1%)
Medication	
5-aminosalicylic acid	95 (92.2%)
Corticosteroids	30 (29.1%)
TNF-alpha antagonist	9 (8.7%)

In terms of disease activity, 48 patients were in endoscopic remission.

Statistically significant differences were recorded between the mean values of CRP, ESR, and Hb on the endoscopic index of activity. Because the calprotectin level was assessed categorially, we could not determine a mean value for different activity levels. Nevertheless, the frequency distribution showed a significant difference between remission and activity (Figure 1).

The Mayo score showed direct, statistically significant correlations with fecal calprotectin, CRP, and ESR (r=0.812, r=0.326, r=0.247, respectively, p<0.05), and an indirect correlation with Hb, but this correlation was not statistically significant (r=–0.148, p=0.139) (Figure 2).

Sensitivity and specificity and the area under the ROC curve were analyzed for each parameter. The cut-off value of 15 µg/g was used for fecal calprotectin; at this value, the inflammation is present.

With an accuracy of 0.909 (confidence interval (CI) = 95%: 0.856–0.962), the ROC curve analysis revealed a sensitivity of 98.0% and a specificity of 76.7%, the best accuracy for

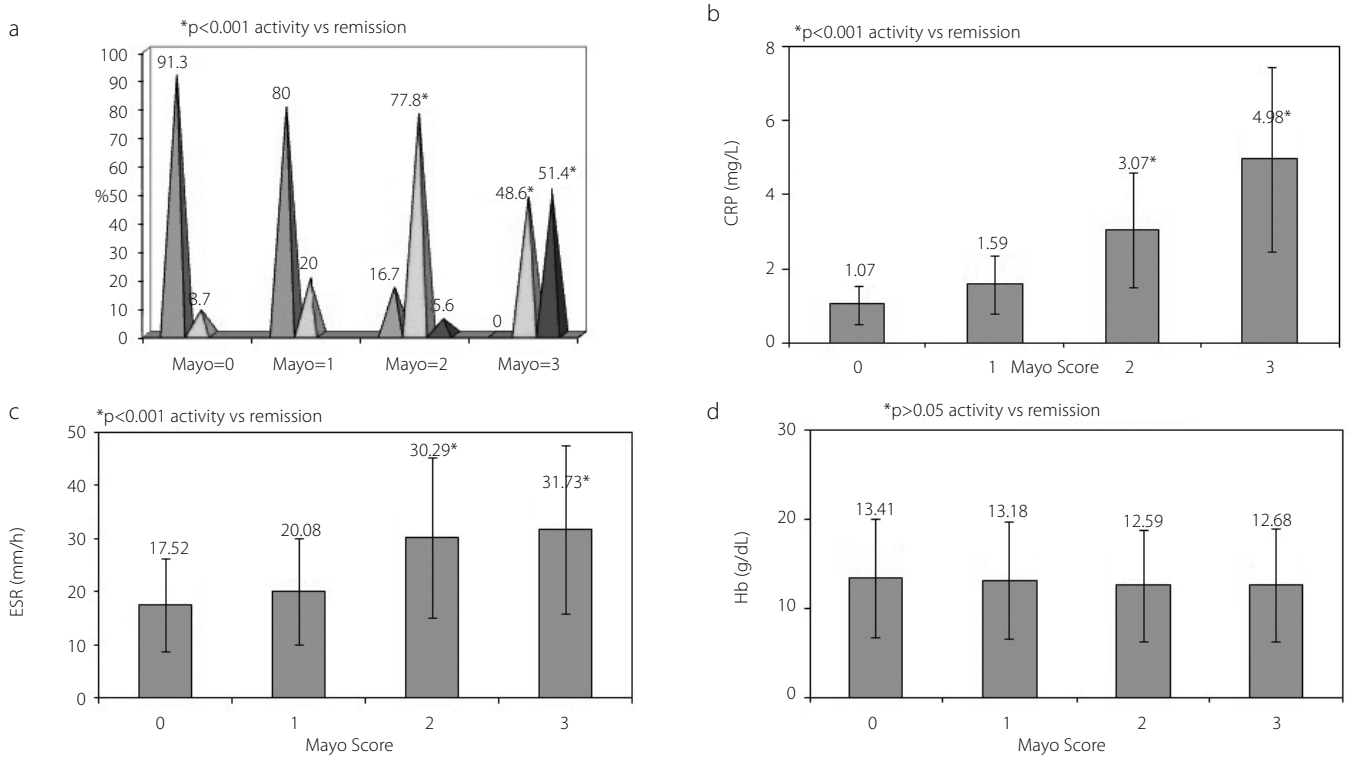

Figure 1. a-d. Concentrations of (a) fecal calprotectin, (b) CRP, (c) ESR, and (d) Hb and the Mayo endoscopic score in UC.
UC: ulcerative colitis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin

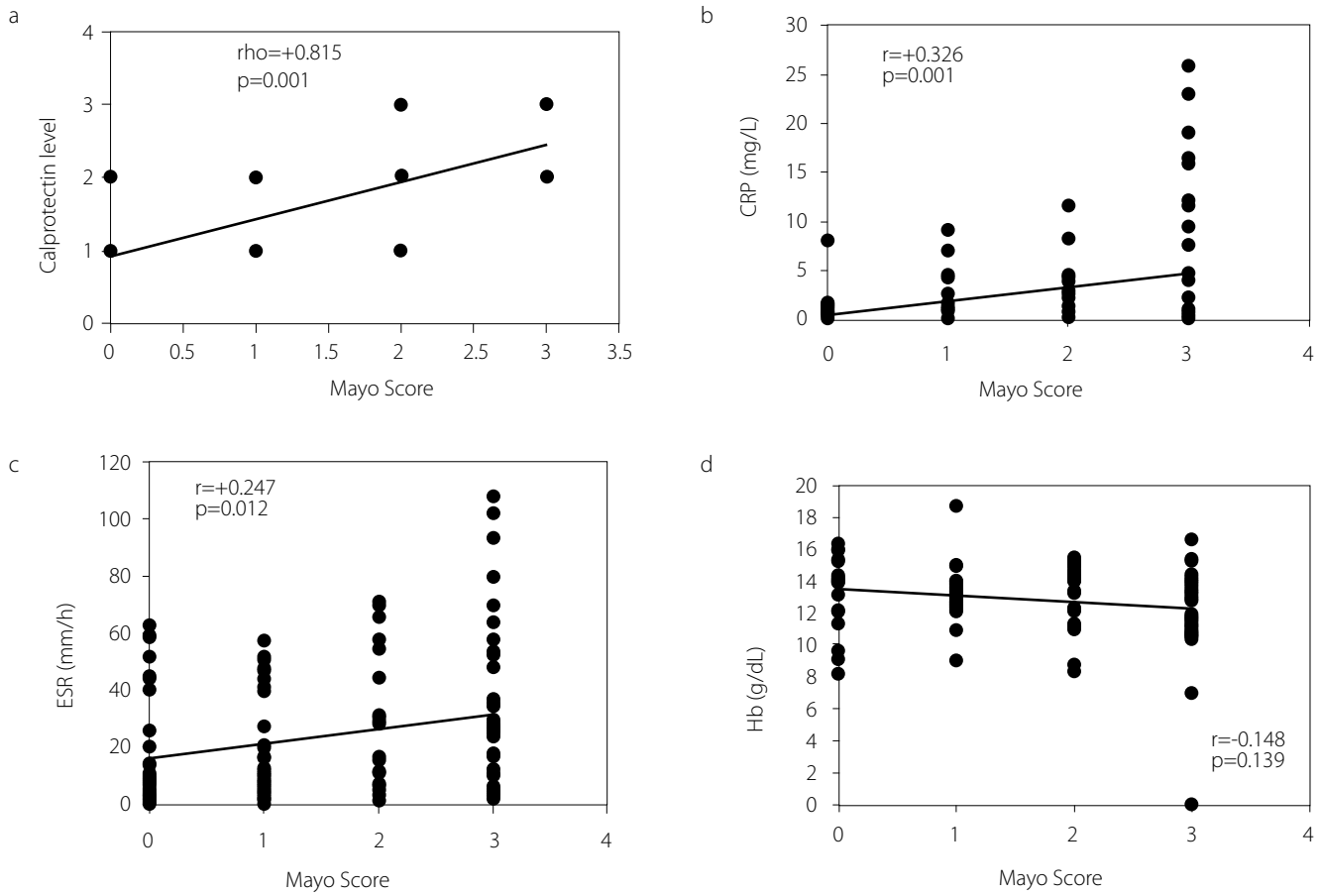

Figure 2. a-d. Correlation between (a) fecal calprotectin, (b) CRP, (c) ESR, and (d) Hb in UC and the Mayo endoscopic score in UC.
UC: ulcerative colitis; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin

Table 2. Sensitivity and specificity for fecal calprotectin, CRP, ESR, and Hb for active endoscopic UC

Variable(s)	Cut-off	Sensitivity (%)	Specificity (%)	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
CRP	0.70 mg/L	69.4	53.0	.602	.064	.091	.477	.726
ESR	12.5 mm/h	61.1	52.0	.597	.060	.105	.480	.714
Hb	13.0 g/dL	50.0	53.0	.459	.062	.493	.338	.580
Calprotectin	15.0 µg/g	98.0	76.7	.909	.027	.000	.856	.962

CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; UC: ulcerative colitis

Table 3. Sensibility and specificity for Hb by sex for active endoscopic UC

Hb	Cut-off	Sensitivity (%)	Specificity (%)	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
Male	13.5 mg/L	50.9	41.2	0.449	0.086	0.529	0.280	0.618
Female	12.5 µg/g	50.0	33.3	0.266	0.143	0.078	–0.014	0.546

Hb: hemoglobin

calprotectin, followed by a CRP efficiency of 0.625 (CI=95%: 0.496–0.784) with a sensitivity of 69.4% and 53.0% specificity. For ESR, the sensitivity and specificity were lower, at 61.1% and 52.0%, respectively, at a cut-off value of 12.5 mm/h determined with an accuracy of 0.666 (CI=95%: 0533–0799). The Hb cut-off value determined in this study was of 13 g/dL. For

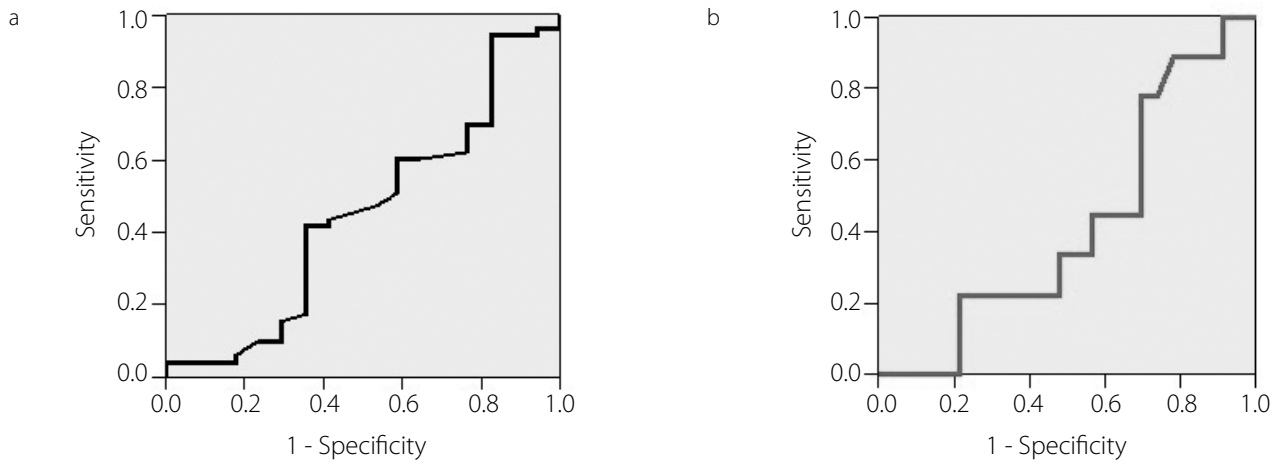

Figure 3. a, b. ROC curve analysis on the Hb ability to distinguish between active UC and inactive UC in (a) male, (b) female.
UC: ulcerative colitis; Hb: hemoglobin

Table 3. Sensibility and specificity for Hb by sex for active endoscopic UC

Hb	Cut-off	Sensitivity (%)	Specificity (%)	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
Male	13.5 mg/L	50.9	41.2	0.449	0.086	0.529	0.280	0.618
Female	12.5 µg/g	50.0	33.3	0.266	0.143	0.078	–0.014	0.546

Hb: hemoglobin

Table 4. Sensitivities, specificities, and predictive values for fecal calprotectin, CRP, ESR, and Hb for active endoscopic disease in UC

Marker	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Accuracy	p
Calprotectin	95.7	46.8	98.0	76.7	90.9	0.001
CRP	95.7	69.8	69.4	52.0	60.2	0.001
ESR	95.7	50.2	61.1	52.0	59.7	0.001
Hb	51.3	56.0	50.0	53.0	45.9	0.001
CRP & ESR	74.5	76.9	84.4	55.0	67.2	0.001
CRP & ESR & Hb	91.3	50.0	80.8	71.4	76.1	0.007
Calprotectin & CRP	89.1	77.8	95.3	64.3	79.8	0.001
Calprotectin & CRP & ESR	95.2	77.8	95.2	77.8	86.5	0.001
Calprotectin & CRP & ESR & Hb	95.2	77.8	95.2	77.8	86.5	0.001

CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin, PPV: positive predictive value; NPV: negative predictive value; UC: ulcerative colitis

this value, the Hb showed a sensitivity of 50.0% and a specificity of 53.0% determined for an efficiency of 0.387 (CI = 95%: 0248–0.526) (Figure 3, Table 2). To improve sensitivity/specificity, we analyzed men and women separately. We did not notice any significant difference between the cumulative and the individual analyses (Table 3, Figure 4). Subsequently, we assessed the combined specificities of the four parameters studied (Table 4).

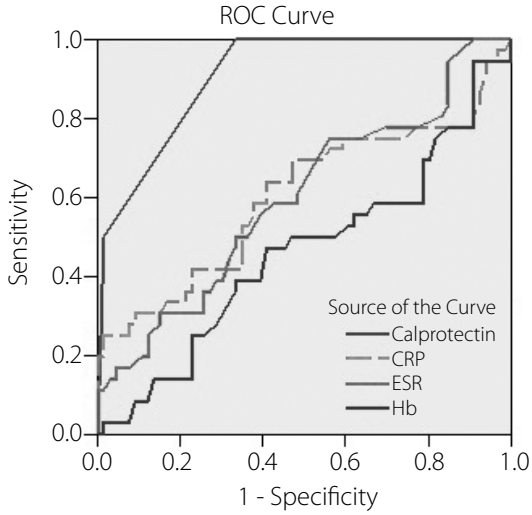

Figure 4. The ROC curve analysis on the abilities of calprotectin, CRP, ESR, and Hb to make a difference between active UC and inactive UC.
UC: ulcerative colitis; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin

DISCUSSION

There are several studies that have investigated the correlation between the biomarkers and the endoscopic indices.

Yoon et al. (12) investigated the correlation between the inflammatory markers and the severity of the endoscopic activity in patients with UC, evaluating over 700 colonoscopies. The study showed good correlation coefficients between CRP

and ESR. For CRP, the correlation coefficient ranged between r=0.457 and r=0.523 and between r=0.342 and r=0.435 for the ESR. At a cut-off value of CRP ≤8 mg/L, sensitivity varied between 50.5% and 53.5% and specificity between 85.1% and 87.2% in detecting remission.

Xiang et al. (13) demonstrated significant correlations between the biological markers [CRP, ESR, acid glycoprotein (AGP)] and the disease activity in UC. For CRP, 62.2% sensitivity and 69.0% specificity were determined at a cut-off value of 5 mg/dl. For ESR, the sensitivity was slightly higher than 64.9%, but with a lower specificity of 68.9%.

In our study, for the cut-off value of CRP ≤7 mg/dL, the sensitivity was 69.4% and specificity was 53.0%. For ESR, lower values of sensitivity and specificity were obtained (61.1% and 52.0%, respectively) at a cut-off value of 12.5 mm/h. The study also showed good correlation coefficients between the CRP and ESR markers and the endoscopic Mayo score.

Anemia is a common complication in IBD. Høivik et al. (14) described a prevalence of 20.2% in patients with UC.

Truelove and Witts introduced anemia severity as a parameter in the classification of UC activity. In a 2007 study, Zezos et al. (15) described a sensitivity of 63% and a specificity of 8.3% and 92% as discrimination Hb between active and inactive disease in patients with recently drug-induced remission and long-term remission, respectively. Our study aimed to analyze the correlation of Hb with disease activity. Given the male dominance in the group study, the resulting cut-off was of 13 g/dL. For this value, using the ROC curve analysis, the Hb had low sensitivity and specificity of just 50.0% and 53.0%, respectively, in discriminating between the endoscopic active disease and remission. The sex-based analysis did not provide any new elements regarding sensitivity/specificity, both preserving low values. This can be explained by the fact that there are several factors that contribute to the appearance of anemia: chronic blood loss, cobalamin deficit, and medication-and not just the inflammatory ones (10).

Fecal calprotectin has been widely studied in recent years as a surrogate marker of IBDs in differential diagnoses, disease progression, or treatment monitoring. The selection method used in most studies was the enzyme-linked immunosorbent assay (ELISA), and the cut-off values established by tests were very diverse (16).

In a recent study on patients with UC, Lobaton Ortega et al. (17) assessed the fecal calprotectin ability to discriminate between different levels of endoscopic activity in 88 patients. The study revealed that at the cut-off level of 250 µg/g, calprotectin presented 94% sensitivity and 80% specificity for endoscopic activity. Jun-Ying Xiang et al. (13) found a sensitivity of 91.9% and a specificity of 79.4% of calprotectin measured by ELISA at the cut-off of 50.0 mg/g as regards the capacity to discriminate between the active and inactive disease.

In 2008, Otten et al. (18) compared a semi-quantitative rapid test similar to the test we used in our study with an ELISA-based test. The Cal Detect® (SOFAR; Florence, Italy) test had a sensitivity of 100% and a specificity of 95% at a cut-off value of 15 µg/g, while the ELISA test had a sensitivity of 96% and a specificity of 87% at a cut-off value of 50 µg/g in discriminating between patients with irritable bowel syndrome and those with IBD.

In our study, we used the cut-off of 15 µg/g, at which the manufacturer estimates the presence of acute inflammation. At this cut-off value, the sensitivity and specificity of calprotectin found in our study were 98.0% and 76.7%, respectively. The ROC curve analysis revealed significantly higher values compared to the rest of the parameters analyzed: CRP, ESR, and Hb. The Cal Detect® (SOFAR; Florence, Italy) test's effectiveness in discriminating between actively and inactively endoscopic disease, assessed by the area under the ROC curve, was 0.909, which confirms its viability for the noninvasive assessment of patients diagnosed with UC.

Sensitivity tends to improve if both biological inflammatory markers (ESR and CRP) are analyzed together. However, specificity also tends to be low, which means that patients in endoscopic remission will need to undergo unnecessary invasive colonoscopies.

Specificity increased when we added Hb to the model, even if we noticed a slight decrease in sensitivity. Even though Hb may be used as an adjunct to ESR and CRP, it has little value when used as a marker of disease activity on its own.

The combined use of calprotectin and CRP leads to an increase in sensitivity compared to the individual use of CRP at 95.3%; however, it drops compared to the individual use of fecal calprotectin, due to the CRP low sensitivity. Although the global sensitivity was very high, the number of false-positive results remained high, with a still low specificity of 63.4%.

Sensitivity remained the same when we added the third inflammatory marker studied, ESR. Moreover, we noticed an increase in specificity to 77.8%, which constitutes an advantage for patients, due to the decrease in the number of unnecessary colonoscopies. Adding Hb to the model did not bring any modification in sensitivity/specificity.

One of the major limitations of the present study was the use of a semi-quantitative test that did not allow us to find a cut-off value for discriminating between active and inactive endoscopic disease or to find mean values for different activity levels. For the same reason, we could not create a mathematical score with noninvasive parameters to appreciate endoscopic

activity in UC. However, the test that we used had the advantages of a very low price comparative with the other tests on the market and the fact that results are instant.

Beside the advantage of limiting unnecessary invasive procedures by using noninvasive markers, the study shows that there is still a small number of patients with endoscopic activity, although the markers are under the cut-off values resulting from the study. This observation leads us to conclude that, at this moment, colonoscopy cannot be replaced completely by the biomarkers that we used, especially for patients with high clinical suspicion.

The main advantage and the novelty of this study is that we used a rapid test for quantifying calprotectin. The test is very easy to use, replicable, and gives instant results. The results obtained from the research shows that this test is very promising in discriminating between endoscopic activity and remission in UC. Running the test does not require laboratory analysis and it can be comfortably carried out in the department, in outpatient clinics, or in medical offices, without the need for special equipment. By using the semi-quantitative rapid test for calprotectin combined with the other noninvasive markers studied, we hope that we can screen better for colonoscopy out-patients.

In conclusion, the semi-quantitative rapid test Cal Detect® (SOFAR; Florence, Italy) proved to be a good predictor test for differentiating between the endoscopic active and inactive disease. Besides this, it is easy to use, replicable, and inexpensive and may be useful in monitoring the UC activity. The other markers analyzed in the study (CRP, ESR, and Hb) did not prove their effectiveness when used individually. The individual use of fecal calprotectin presents the highest sensitivity in determining the endoscopic activity. Nevertheless, in monitoring patients, the combined determination of the three inflammatory markers studied (CRP, ESR, and calprotectin) is more useful in reducing the number of false-positive values and, implicitly, the unnecessary colonoscopies, or treatment change.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.D., C.C.P.; Design - M.D.; Supervision - C.M., V.D, C.C.P.; Data Collection and/or Processing - M.D., G.D.; Analysis and/or Interpretation - M.D.; Literature Review - M.D.; Writer - M.D.; Critical Review - C.M., C.C.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Bamias G, Kaltsa G, Ladas SD. Cytokines in the pathogenesis of ulcerative colitis. Discovery Medicine 2011; 11: 459-67.
2. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012; 380: 1606-17. [CrossRef]
3. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-Elastase, CRP, and Clinical Indice. Am J Gastroenterol 2008; 103: 162-9. [CrossRef]
4. Vermeire S, Van Assche G, Rutgeerts P. C-Reactive Protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004; 10: 661-5. [CrossRef]
5. Solem CA, Loftus EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005; 11: 707-12. [CrossRef]
6. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys. Gut 2006; 55: 426-31. [CrossRef]
7. Gabay C, Kushner I. Acute phase reactants and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-54. [CrossRef]
8. Sachar DB, Smith H, Chan S, Cohen LB, Lichtiger S, Messer J. Erythrocytic sedimentation rate as a measure of clinical activity in inflammatory bowel disease. J Clin Gastroenterol 1986; 8: 647-50. [CrossRef]
9. Osada T, Ohkusa T, Okayasu I, et al. Correlation among total colonoscopic findings, clinical symptoms, and laboratory markers in ulcerative colitis. J Gastroenterol Hepatol 2008; 23: S262-7. [CrossRef]
10. Gasche C, Lomer MCE, Cavill I, Weiss G. Iron, anemia, and inflammatory bowel diseases. Gut 2004; 53: 1190-7. [CrossRef]
11. Kopylov U, Rosenfeld G, Bressler B, Seidman E. Clinical utility of fecal biomarkers for the diagnosis and management of inflammatory bowel disease. Inflamm Bowel Dis 2014; 20: 742-56. [CrossRef]
12. Yoon JJ, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Correlation of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic indices in patients with ulcerative colitis. Dig Dis Sci 2014; 59: 706-7. [CrossRef]
13. Xiang JY, Ouyang Q, Li GD, Xiao NP. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. World J Gastroenterol 2008; 14: 53-7. [CrossRef]
14. Høivik ML, Reinisch W, Cvancarova M, Moum B; IBSEN study group. Anemia in inflammatory bowel disease: a population-based 10-year follow-up. Aliment Pharmacol Ther 2014; 39: 69-76. [CrossRef]
15. Zezos P, Papaioannou G, Nikolaidis N, et al. The value of inflammation and coagulation markers for the assessment of the activity and clinical outcome of ulcerative colitis. Ann Gastroenterol 2007; 20: 207-17.
16. Lin JF, Chen JM, Zuo JH, et al. Meta-analysis: Fecal Calprotectin for Assessment of Inflammatory Bowel Disease Activity. Inflamm Bowel Dis 2014; 20: 1407-15. [CrossRef]
17. Lobaton Ortega T, Rodriguez-Moranta F, Guardiola J. P025. A new rapid test for fecal calprotectin (FC) predicts mucosal healing in ulcerative colitis (UC). European Crohn's and Colitis Organisation, Conference 2013.
18. Otten CMT, Kok L, Witteman BJM, et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. Clin Chem Lab Med 2008; 46: 1275-80. [CrossRef]