Research Article

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Crohn's disease activity evaluation based on imaging studies and biomarkers

Abstract

Background and aims: Crohn's disease (CD) is a chronic condition with a variable course. Available grading systems include clinical assessment using CDAI scale, imaging studies and biomarkers. The aim of this study is to determine the suitability of available diagnostic methods, by means of comparison, for predicting the disease activity, based on cost efficiency and sensitivity criteria.

Materials and methods: In this study, we conducted analyses of 37 patients with CD. Crohn's disease was graded as "active" or "inactive" by adopting certain cut off values for every marker.

The main assumption was that methods used to grade CD severity (Endoscopy SESCD scale, MRI enterography: DWI ADC, CRP and Calprotectine) do not give false positive results. In addition none of these methods was considered a reference method. Authors also decided to measure the agreement between the methods by applying the Cohen's Kappa coefficient and compare them to the CDAI method.

Results: Endoscopy shows the highest sensitivity, NPV and accuracy in detecting activity of CD overall and in each intestine separately. In the case of involvement of both intestines, the sensitivity of endoscopy reached 93.9 % and the accuracy 94.6%, while the sensitivity and accuracy of enterography and calprotectin were 51.5% vs. 71.9% and 56.8% vs. 72.2%, respectively. For the large intestine, the sensitivity and accuracy of endoscopy reached 100.0%. This means that there were no cases when enterography detected the activity of disease and endoscopy did not. For the small intestine, the sensitivity of endoscopy was 55.0% and accuracy 75.0%, while enterography showed only 66.7% and 81.1% respectively. The best agreement (77.1%), taking into account all pairs of methods, and the only one which proved to be statistically important (p=0.005) was between endoscopy and calprotectin regarding the involvement of both small and large intestine. However, the value of Cohen's Kappa suggest that this agreement is rather moderate. The optimal cut- off value for calprotectin was 43.0µg/g for both techniques (Tangent method and Youden's index). Area under the ROC curve (AUC=0.871) was large enough to conclude that calprotectin is a statistically significant (p<0.001) indicator of CD activity in both small and large intestine.

Conclusion: Statistically significant compliance was shown only between colonoscopy and fecal calprotectin.

Keywords: biomarkers, imaging, crohn's disease, CDAI, CRP, MRE, SES-CD, fecal calprotectin

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Introduction

Inflammatory bowel diseases like Crohn's disease or ulcerative colitis represent a group of chronic conditions characterized by periods of flare-ups and remissions. In the Northern Hemisphere, the incidence rate of Crohn's disease amounts to 1-10 per 100.000 people, whereas the prevalence rate is estimated at 1-0.5 per 1.000 people. Therefore, Crohn's disease is not considered a rare condition in neither Europe nor North America.[1]

The therapeutic goal of the IBD treatment is not only to achieve a clinical remission, but also to induce mucosal healing, which contributes to a long-term remission. The monitoring of patients with inflammatory bowel diseases should be optimized in such a way as to identify the activity of the disease at its subclinical stage, and consequently modify the treatment, taking into consideration costs. Currently, different methods are used to assess the activity of the disease, including: Crohn's Disease Activity Index (CDAI), inflammatory biomarkers and medical imaging, which shows the severity of inflammatory changes.

Crohn's Disease Activity Index (CDAI) is considered the golden standard for assessing the clinical condition of patients. According to the ECCO guidelines, a CDAI score <150.0 points indicates a remission, whereas a CDAI score>220.0 points indicates disease exacerbation.[2] Biomarkers used in laboratory tests include: C-reactive protein (CRP), hemoglobin, leukocytes, thrombocytes, serum iron, ferritin, ceruloplasmin, alpha1-antitripsin, plasminogen, fibrinogen, interleukin 6, salicylic acid and amyloid A.[3] Fecal biomarkers include: fecal calprotectin (FC), fecal lactoferrin (FL), elastase, myeloperoxidase, metalloproteinase 9 and neoprotein.[4]

CRP, a protein produced by hepatocytes, is not characteristic solely of IBD. The CRP level is elevated in other inflammatory diseases as well.[5,6] In IBD, the CRP level should be measured along with other markers, such as erythrocytes, hemoglobin and albumins.[7] In addition, high CRP levels are more often seen in transmural pattern of inflammation (Crohn's disease), rather than in ulcerative colitis.[8–10]

There is a correlation between elevated CRP levels and the clinical activity of CD,[7,11,12] however in 20.0-25.0% of patients with severe

CD, there is no increase in the CRP level due to a single-nucleotide polymorphism in the CRP gene.[13] The cut-off value for CRP in inflammatory bowel diseases should be >5.0mg/dl, which is also related to the activity of the disease in the endoscopic evaluation.[14] Fecal calprotectin (FC) is an inflammatory protein found in the cytosol of human neutrophils, macrophages and monocytes.[15,16] When inflammation is present, the FC level is in direct proportion to the migration of neutrophils to the digestive tract. This is the reason for increased levels of FC in case of inflammatory diseases of the digestive tract in general.

Furthermore, it seems that the FC level correlates with histologic results and therefore can serve as a predictor of relapse.[17] According to a study, the median FC level in patients with relapses was 414.0 µg/g, compared to 96.0 µg/g in patients without a relapse ($p<0.005$). However, the FC level of 240.0 µg/g was a predictor of relapse within 12 month period.[18] Therefore, CRP and FC are recognized markers for assessing the subclinical activity of IBD. CRP is an easy and fast biochemical parameter to measure, however there is a poor correlation with clinical and endoscopic assessments.[13] FC is a more expensive, but also more specific parameter of inflammation activity, and has a better correlation with the endoscopic assessment (excluding isolated changes in the small intestine). The FC level below 50.0 mg/g indicates an inactive process. Different methods of assessing FC may generate different results, varying from 7.8% to 28.1%.[18]

Consequently, a further observation is required in order to compare FC levels with endoscopic images, due to the fact that in different studies the FC level was measured at different time intervals with reference to colonoscopy, which makes it more difficult to determine the cut-off value of this biomarker. The FC level for isolated changes in the small intestine are lower, and therefore, its predictive value should be lower compared to the large intestine. Thus, if the FC level below 50.0 µg/g indicates a remission, whereas the FC level above 250.0 µg/g suggests disease activity, one has to question how to interpret other borderline values.[19,20]

Magnetic resonance enterography (MRE), an examination used for visualizing small intestine damage, is an important complementary test to colonoscopy. Along with biochemical endoscopic assessments, MRE is used to diagnose and assess the activity of IBD; nevertheless, ileocolonoscopy with biopsy still remains the first-line diagnostic tool.[21–23] MRE and CTE (computed tomography enterography) are imaging techniques used to investigate intramural changes and complications of CD.[24–26]

Taking into consideration the onset of CD in patients, its chronic character, recurrence, frequent involvement of the small intestine and the risk of developing complications, it seems necessary to repeat imaging examinations, especially MRE, in patients with IBD.[27–29] MRE is recommended by ECCO, not only as a diagnostic tool, but also as a monitoring tool in patients with CD.[22,23] It also determines the choice of treatment: conservative or surgical.[30,31]

A comparison study conducted to evaluate the diagnostic value of MRE and ileocolonoscopy in monitoring the response to treatment in patients with CD showed that both methods have a similar degree of reliability when it comes to assessing the healing of changes (90.0% vs. 83.0%).[32]

Colonoscopy is a recommended method for assessing the disease activity in the large intestine and the distal segment of the ileum. Currently, two methods are applied to assess the inflammation: SES-CD (Simple Endoscopic Score Index) and CDEIS (Crohn's Disease Index of Severity).[33] Both methods involve the use of video colonoscopy. In the SES-CD system, five bowel segments are examined, and values ranging from 0 to 3 are given to each segment, taking into consideration the following variables: ulcerated surface, size of ulcers, affected surface and narrowings.[34]

The study described in this article was performed to assess and compare methods used for the assessment of inflammation activity in CD, such as: blood and fecal biomarkers, imaging techniques and clinical assessment based on CDAI. The aim of the study was to determine which method is the most accurate and therefore could be used to optimize the monitoring of patients, as well as to modify the currently used methods of treatment.

Material and methods

Study design

The study enrolled 37 patients with Crohn's disease hospitalized in the Department of Gastroenterology of the Self-Dependent Health Care Unit of Ministry of Interioir in Gdańsk in 2015-2017 to assess CD activity based on CDAI, blood biomarkers (hemoglobin, thrombocytes, iron, CRP), fecal biomarker (calprotectin) and imaging techniques (ileocolonoscopy and magnetic resonance enterography).

Tests were conducted at a one-week interval between imaging examinations, and other laboratory analyzes were performed at a single stage, 24 hours before colonoscopy. The CDAI calculator take into consideration: sex, weight, height, age, hematocrit, presence of abdominal masses, extra-intestinal complications, anti-diarrhea drug use, number of soft/liquid stools, severity of abdominal pain and patient's general well-being.

Crohn's disease may be active or inactive. The cut-off values were set at the CDAI score ≤150.0 for the inactive disease and at the CDAI score >150.0 for the active disease. An immunoturbidymetric method was used to assay serum CRP, which is a test for quantitative determination with high sensitivity, using antibodies coated on latex, against this human acute phase protein.[35] The cut-off value of 5.0 mg/dl was set to differentiate between the active disease (above the cut-off level and inactive disease (below the cut-off level).

Fecal calprotectin was measured using the Quantum Blue Calprotectic test for the quantitative measurement of calprotectin level in fecal samples. Stool samples were stored in a refrigerator at 2.0-8.0°C and examined within 24 hours, similarly to specimen tubes. Both stool samples and specimen tubes were stored at room temperature of 24.0±4.0°C for 20.0 minutes before the procedure. Next, each stool sample was disrupted and dissolved in an extraction buffer. An automatic pipette was used to collect fecal specimen, which was then inserted into a separate specimen tube and dissolved in the "Chase buffer" in a 1:15 ratio (20.0µl of the specimen + 280.0µl of the buffer). The reader was calibrated to an extended range (30.0-1800.0µg/g) and the fecal extract of 60.0µl was loaded onto the loading port of the test cassette. After 12.0 minutes of incubation, the extract was put in the tray. The test cassette was automatically read and the result was displayed on a screen. The cut-off value was set at 100.0µg/g for disease activity.

In ileocolonoscopy, a SES-CD score was used to assess the disease activity. Five bowel segments were examined and the following criteria were used to assess the severity of the disease: Table 1.

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Table 1 Simple endoscopic score (SES-CD)

Variable	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<5 0%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD=Sum of all variables for the 5 bowel segments. Values are given to each variable for every examined bowel segment[34]

Adding the scores from all five segments assessed the disease activity. The final score was interpreted in the following manner:

≤2.0: inactive CD

3.0-6.0: mild CD

7.0-15.0: moderate CD

>16.0: severe CD

For the purposes of this study, the score ≤2.0 points was considered indicative of an inactive inflammation process. Scores above 2.0 points, on the other hand, were indicative of an active inflammation process. In MRE, the disease activity was assessed as active or inactive (by assessing the location of changes and the severity of the inflammation process) in the small and large intestine, based on the following examination protocol: before the examination, a patient is asked to drink approx. 1.5 1 of 3.0% mannitol solution over 60 minutes. During the examination, a contrast agent is administered (ProHance or Gadovist), and the following sequences are analyzed according to the protocol:

i. **T2 haste cor**

Slice 3.5 mm gap 0.0 mm

TR 1200.0 ms TE 100.0 ms

Matrix 288.0x384.0

ii. **T2 haste stir cor**

Slice 4.0 mm gap 0.0 mm

TR 1200.0 ms TE 100.0 ms TI 180.0 ms

Matrix 288.0x384.0

iii. **T2 trufi cor**

Slice 4.0 mm gap 0.0 mm

TR 3.51 ms TE 1.45 ms

Matrix 167.0x256.0

iv. **DWI cor**

Slice 5.0 mm gap 0.0 mm

TR 6400.0 ms TE 65.0 ms

Matrix 160.0x160.0

b=0, 50, 500, 800

v. **T2 haste tra**

Slice 4.0 mm gap 0.0 mm

TR 1200.0 ms TE 102.0 ms

Matrix 260.0x320.0

vi. **T1 flash tra**

Slice 4.0 mm gap 0.8 mm

TR 189.0 ms TE 4.93 ms

Matrix 203.0x320.0

vii. **T1 vibe fs cor dynamika CM**

Slice 3.0 mm gap 0.6 mm

TR 4.36 ms TE 1.92 ms

Matrix 183.0x288.0

Dynamik – 8.0

8. T1 flash fs tra

Slice 4.0 mm gap 0.8 mm

TR 145.0 ms TE 2.38 ms

matrix 167.0x256.0

Statistical analysis

All data were compared by means of statistical analysis to determine the correlation between them and, at the same time, to identify the usefulness of particular markers of disease activity with reference to their sensitivity, specificity, as well as reliability, which has an impact on retesting and economic aspects of different tests. The main assumption of the analysis was that methods used to detect Crohn's disease activity (CDAI, Endoscopy, Enterography and Calprotectine) do not give false positive results. Moreover, none of these methods was considered a reference method. The true positive conditions were defined when either of the methods yielded a positive result. In other words, true negative conditions were specified when an investigation by all three methods brought a negative result. This implied that specificity and PPV (positive predictive value) were equal to 100.0%. Therefore, the comparison of methods presented in the article was based on sensitivity, NPV (negative predictive value) and accuracy. The authors also decided to measure the agreement between all methods based on the Cohen's Kappa coefficient and compare them to the CDAI based method.

Additionally, an optimal cut-off value was set, for calprotectin, based on the ROC curve, with the use of two techniques: tangent method and Youden index. Finally, all comparative analyses were performed separately for the small and large intestine, when possible.

The level of significance was set at α=0.05 and all statistical

analyses were performed using Statistica version 12.5.

The analysis was based on the following assumptions:

a. There is no golden standard when it comes to detecting the disease activity in the small and large intestine,

b. Methods based on endoscopy and enterography have a positive predictive value (PPV=100.0%), which means that if a patient is diagnosed with an active disease, the diagnosis is 100.0% certain – there are no false positive results (Specificity=100.0%).

A variable was defined as, "Reality," which showed whether the disease is active, i.e. whether any of the two imaging techniques (Endoscopy or Enterography) revealed the activity of the disease.

It was assumed that:

a. CDAI score >150.0 points indicates disease activity,

b. SES-CD score >2.0 points indicates disease activity,

c. CRP level >5.0 mg/dl indicates disease activity,

d. Calprotectin level >100.0μg/g indicates disease activity.

Results

Approach no 1

When the disease activity is assessed without dividing the intestine into segments – i.e. in the small and large intestine as a whole – it means that the disease is considered active, if it occurs in any of the two bowel segments (Table 2).

Table 2 Endoscopy

Observed frequency		Reality	
		Active	**Inactive**
Ileocolonoscopy	Active	31	0
	Inactive	2	4
	Total	33	4

Sensitivity=93.9%, Specificity=100.0%, PPV=100.0%, NPV=66.7%, ACC=94.6%

This means that in 93.9% of patients, the disease activity was detected correctly

100.0% of patients who have no disease activity have been detected by endoscopy

The patient diagnosed with the disease activity has it on 100.0%

The patient diagnosed with inactivity does not have 66.7%

The diagnosis for the patient (regardless of the result) by the endoscopy is accurate in 94.6%

Table 3: In 51.5% of patients, the disease activity was correctly detected

100.0% of patients who have no disease activity were detected by enterography

The patient diagnosed with the disease activity has it on 100.0%

The patient diagnosed with inactivity does not have 20.0%

Diagnosis for the patient (regardless of the result) adopted according to the MRE study is accurate in 56.8%

Table 4: In 71.9% of patients, the disease activity was correctly detected

Table 3 MRI

Observed frequency		Reality	
		Active	**Inactive**
MR Enterography	Active	17	0
	Inactive	16	4
	Total	33	4

Sensitivity=51.5%, Specificity=100.0%, PPV=100.0%, NPV=20.0%, ACC = 56.8%

Table 4 Calprotectin

Observed frequency		Reality	
		Active	**Inactive**
Fecal calprotectin	Active	24	1
	Inactive	9	3
	Total	33	4

Sensitivity=71.9%, Specificity=75.0%, PPV=95.8%, NPV=25.0%, ACC=72.2%

75.0% of patients who have no disease activity have been detected by calprotectin

The patient diagnosed with the disease activity has 95.8%

A patient diagnosed with inactivity does not have 25.0%

The diagnosis for the patient (regardless of the result) by calprotectin is accurate in 75.0%

Table 5: Among patients with active disease, 58.8% of cases were detected correctly.

Table 5 CRP

Observed frequency		Reality (for both intestines)	
		Active	**Inactive**
CRP	Active	20	0
	Inactive	14	3
	Total	34	3

Sensitivity=58.8%, Specificity=100.0%, PPV=100.0%, NPV=22.2%, ACC=63.2%

100.0% of patients who have no disease activity were supported by CRP

The patient diagnosed with the disease activity has it on 100.0%

The patient diagnosed with lack of activity does not have 22.2%

The diagnosis for a patient based on the threshold value of CRP is accurate in 63.2%

Table 5: In 76.5% of patients, the disease activity was correctly detected

25.0% of patients who have no disease activity have been determined by CDAI

The patient diagnosed with the disease activity has it at 89.7%

A patient diagnosed with inactivity does not have 11.0%

The diagnosis for the patient (regardless of the result) by CDAI is accurate in 71.1%

Table 6 CDAI

Observed frequency		Reality	
		Active	**Inactive**
CDAI	Active	25	3
	Inactive	8	1
	Total	33	4

Sensitivity=76.5%, Specificity=25.0%, PPV=89.7%, NPV=11.1%, ACC=71.1%

Approach no 2

If we treat the assessment of disease activity separately, i.e. we will analyze these exponents separately for changes in the small intestine and separately for changes in the large intestine, the statistical evaluation of the diagnostic methods used will be as follows:

Small intestine

Table 7: In 55.0% of patients, the activity of the disease in the small intestine was correctly detected.

Table 7 Endoscopy

Observed frequency		Reality	
		Active	**Inactive**
Endoscopy (small intestine)	Active	12	0
	Inactive	9	16
	Total	21	16

Sensitivity=55.0%, Specificity=100.0%, PPV=100.0%, NPV=64.0%, ACC=75.0%

100.0% of patients who have no disease activity have been detected by endoscopy

The patient diagnosed with the disease activity has it on 100.0%

The patient diagnosed with inactivity does not have 64.0%

Diagnosis for the patient (regardless of the result) through the use of endoscopy is accurate in 75.0%.

Table 8: In 66.7% of patients, the activity of the disease in the small intestine was correctly detected.

Table 8 MRI

Observed frequency		Reality	
		Active	**Inactive**
MR Enterography (small intestine)	Active	14	0
	Inactive	7	16
	Total	21	16

Sensitivity = 66.7%, Specificity=100.0%, PPV = 100.0%, NPV=69.6%, ACC=81.1%,

100.0% of patients who have no disease activity were detected by enterography

The patient diagnosed with the disease activity has it on 100.0%

A patient diagnosed with inactivity does not have 69.6%

Diagnosis for the patient (regardless of the outcome) evaluated in the MRI enterografis is accurate in 81.1%.

Table 9: Among patients with active disease, 66.7% of cases were detected correctly.

Table 9 CRP

Observed frequency		Reality	
		Active	**Inactive**
CRP (small intestine)	Active	14	5
	Inactive	7	11
	Total	21	16

Sensitivity=66.7%, Specificity=68.8%, PPV=73.7%, NPV=61.1%, ACC=67.6%,

68.8% of patients who have no disease activity were supported by CRP

The patient diagnosed with the disease activity has it on 73.7%

A patient diagnosed with a lack of activity does not have it on 61.1%

The diagnosis for the patient based on the threshold value of CRP is accurate in 67.6%

Large intestine

Table 10: In 96.4% of patients, the disease activity in the large intestine was correctly detected

Table 10 Endoscopy

Observed frequency		Reality	
		Active	**Inactive**
Endoscopy (large intestine)	Active	27	0
	Inactive	1	9
	Total	28	9

Sensitivity=96.4%, Specificity=100.0%, PPV=100.0%, NPV=90.0%, ACC=97.3%

100.0% of patients who have no disease activity were detected in the endoscopic examination – colonoscopy

The patient diagnosed with the disease activity has it on 100.0%

The patient diagnosed with inactivity does not have 90.0%

Diagnosis for a patient (regardless of the result) after a colonoscopy is accurate in 97.3%.

Table 11: In case of 33.3% of patients, the disease activity in the area of large intestine was correctly detected

100.0% of patients in whom no disease activity was detected have MR enterographies

The patient diagnosed with the disease activity has it on 100.0%

A patient diagnosed with inactivity does not have 33.3%

Table 11 MRI

Observed frequency		Reality	
		Active	Inactive
MR Enterography (large intestine)	Active	9	0
	Inactive	19	9
	Total	28	9

Sensitivity=33.3%, Specificity = 100.0%, PPV=100.0%, NPV=33.3%,ACC=50.0%

Diagnosis for the patient (regardless of the result) pasted with the use of enterography MR is accurate in 50.0%.

Table 12: Among patients with active disease, 64.3% of cases were detected correctly.

Table 12 CRP

Observed frequency		Reality	
		Active	Inactive
CRP (large intestine)	Active	18	1
	Inactive	10	8
	Total	28	9

Sensitivity=64.3%, Specificity=88.9%, PPV=94.7%, NPV=44.4%, ACC=70.3%

88.9% of patients who have no disease activity were supported by CRP

The patient diagnosed with the disease activity has 94.7%

A patient diagnosed with inactivity does not have 44.4%

The diagnosis for a patient based on the CRP threshold is accurate in 70.3%

Agreement of methods

The agreement of methods was assessed using an unadjusted coefficient of agreement and the Cohen's Kappa coefficient (Table 13). A statistically significant agreement of methods was identified in the case of Endoscopy and Calprotectin, as well as CRP values and CDAI values. There was a correlation between CRP and Calprotectin, CRP and Enterography of the small intestine and CRP and colonoscopy of the large intestine.

Calprotectin cut-off values

Calprotectin shows a high degree of effectiveness in the detection of CD activity in the large intestine and the bowel in general. However, the level of this biomarker should not be used for assessment of the disease activity solely within the small intestine (Figure 1) (Table 14).

According to the Youden Index, the cut-off value of 100.0µg/g (sensitivity = 88.9%, specificity=87.5%) and 43.0µg/g (sensitivity=93.8%, specificity=75.0%) should be used for the large intestine and a full-scope detection respectively.

Table 13 Agreement of methods

Compared methods		Coefficient of agreement	Cohen's Kappa	p-value
		50.00%	0.069	0.549
Ileocolonoscopy	MR Enterography			
Ileocolonoscopy	Fecal calprotectin	77.10%	0.424	0.005
MR Enterography	Fecal calprotectin	54.30%	0.094	0.555
CDAI	Ileocolonoscopy	52.60%	-0.305	0.179
CDAI	MR Enterography	57.90%	0.283	0.078
CDAI	Fecal calprotectin	52.90%	0.029	0.893
Endoscopy (small intestine)	MR Enterography (small intestine)	57.90%	0.038	0.865
Endoscopy	MR Enterography	47.40%	0.159	0.2
(large intestine)	(large intestine)			
CRP	Ileocolonoscopy	67.60%	0.339	0.006
CRP	MR Enterography	67.60%	0.353	0.031
CRP	Fecal Calprotectin	72.20%	0.423	0.009
CRP	CDAI	76.30%	0.513	<0.001
CRP	Endoscopy (small intestine)	62.20%	0.251	0.091

Table 14 Calprotectin values

Scope	Cut-off values according to		AUC	p-value
	Tangent method	Youden Index		
Small and large intestine	43	43	0.871	p<0.001
Small intestine	61	61	0.439	0.549
Large intestine	63	100	0.944	p<0.001

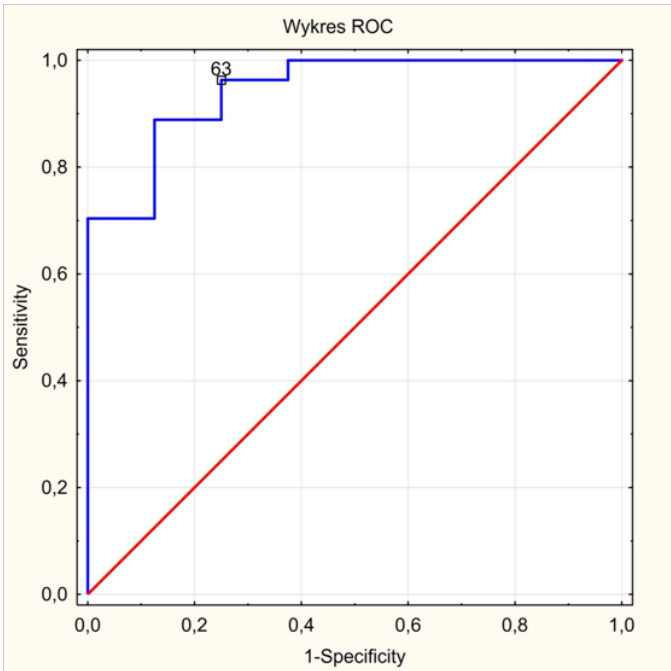

Figure 1 ROC curve for Calprotectin.

Discussion

Recently, the clinical management of patient with IBD has evolved, with the main aim now being not only a clinical remission, but also mucosal healing.

Therefore, it is necessary to monitor the disease activity in order to detect it at its early subclinical stage, as well as taking the cost into account.

In this study, the following testing methods were assessed:

Clinical evaluation of CDAI disease activity,

Biomarkers: fecal calprotectin and serum CRP,

Imaging examinations: ileocolonoscopy, MR enterography.

Since CD is a disease of the gastrointestinal system, the effectiveness of these tests was examined both comprehensively (in the two bowels) and in the small or large intestine separately, depending on the disease activity. Diagnostic tests were assessed in terms of their sensitivity and specificity, and in addition they were also compared to each other in order to specify which test is the most effective in quantitating CD activity, taking into consideration the fact that 20.0% of patients experience early relapses.

The current golden standard in assessing the disease activity is the CDAI system.

According to the ECCO consensus, a clinical remission can be diagnosed when the CDAI score is below 150.0 points. The disease is active when a patient scores more than 220.0 points.[2] However, this index is often criticized for being too subjective.

In our study, the sensitivity of this method (with a cut-off value of 150.0 points) was 76.5%, whereas the specificity – a mere 25.0%. The predictive positive value (PPV) was 89.7% and the predictive negative value (PNV) was 11.1%. The accuracy of this method (ACC), which reflects the correct diagnosis of a patient regardless of the findings, was 71.1%. This can be set in comparison to a study where CDAI was set against mucosal healing, defined as the lack of ulceration, and where the cut-off value for the disease activity was 150.0 points, PPV amounted to 65.0% and NPV – to 53.0%. Another parameter that was investigated was CPR, which is a relatively cheap and quick method of assessing CD activity. The activity of the disease correlated with the CPR level,[7,11,12] but it is important to have in mind that in 20.0-25.0% of patients with severe CD, there is no CRP elevation.

In our study, the cut-off value for the process of inflammation was set at the CRP level of 5.0 mg/dl. It was demonstrated that when assessing this parameter in patients with changes limited to the small intestine, the sensitivity and specificity amounted to 66.7% and 68.8% respectively. PPV and NPV were at the level of 73.3% and 67.6% respectively, whereas the accuracy was estimated at 67.6%. In the case of changes within the large intestine, the sensitivity and specificity of this method was estimated at 64.3% and 88.0% respectively, with PPV and NPV amounting to 94.7% and 44.4% respectively. The accuracy of the method was 70.3%. Without differentiating the range of inflammatory changes, the sensitivity of the method was calculated at 58.8% with a 100.0% specificity, whereas PPV and NPV stood at 100.0% and 22.2% respectively. In this case, the accuracy was estimated at 33.2%.

In a study by Solem et al.,[7] it was shown that CPR <5.0 mg/dl with a normal endoscopic appearance of the intestinal mucosa is found in 75.0% of cases, and the elevated CPR level correlated with inflammatory changes. However, another study (36) showed that isolated changes in the ileum correspond with high CPR values. Mosli et al.[14] conducted a meta-analysis of 19 studies (n=2499 patients with IBD), in which the CRP level was compared with the endoscopic appearance of the mucosa. The sensitivity and specificity of this parameter was calculated at 49% and 92% respectively, and it was suggested that CPR >5.0 mg/dl may indicate an endoscopic inflammatory activity.

Another biomarker, fecal calprotectin (FC), is in proportion to the migration of neutrophils to the digestive tract during an ongoing process of inflammation.[5,6,36] Besides, FC seems to correlate with the endoscopic and histologic appearance of the mucosa and may be used as a predictor of relapse.[5,17]

In our study, the sensitivity and specificity of fecal calprotectin was calculated at 71.9% and 75.0%, with PPV and NPV of 95.8% and 25.0% respectively. The accuracy (ACC) of this method was estimated at 72.2%. The cut-off value of calprotectin was also determined, depending on the disease activity, which was 43.0µg/g for the small intestine and 100.0µg/g for the large intestine (p<0.0001). The area under the curve (ROC AUC) was 0.87 without differentiating the range of changes and 0.944 for the FC value of 100.0µg/g in the case of the large intestine.

In a study by Mosli et al.,[14] the FC biomarker demonstrated a higher sensitivity in determining the disease activity than CRP. The sensitivity and specificity of this biomarker in CD were 87.0% and 67.0% respectively, with a cut-off value of 50.0µg/g. In a study by D'Haens et al.,[34] the greatest ROC AUC was found by the cut-off value of 250.0µg/g, which correlated with an endoscopic remission (CDEIS <3.0 points). The sensitivity and specificity were calculated at 94.1% and 62.2%.[38,39] The study by Rostek et al.[40] showed that the FC level <50.0µg/g correlates with a full remission on ileocolonoscopy.

The FC sensitivity and specificity was also assessed in relation to changes found during capsule endoscopy. However, the correlation was rather low – 59.0% and 71.0% respectively.[41] FC values for changes in the small intestine were lower than for changes in the large intestine, but there was a correlation between FC an SES-CD ($p<0.0001$),[42] similarly to a study by Schopter et al.,[43] where this correlation occurred between the distal segment of the ileum and the FC level.[43] The analysis we conducted also showed a difference in the FC value for the activity of the inflammatory process in the small intestine and large intestine, with simultaneous correlation of the endoscopic image with the value of this biomarker. In our study, FC the cut-off value used for the inflammation activity was 43.0µg/g for CD (ACU 0.87) and 100.0µg/g in the case of changes limited only to the large intestine (ACU 0.944).

When it comes to the level of FC that predisposes patients to an endoscopic remission, the value varies from study to study. In one study, the sensitivity and specificity of the test was 94.0% and 62.0% respectively, with a predicting value of 250.0µg/g.[13] In another study, in which the predicting value was set at 200.0µg/g, the sensitivity and specificity was calculated at 70.0% and 92.0% respectively.[44] Yet another study, in which the predicting value was 70.0µg/g, showed that the sensitivity and specificity in examining the process of inflammation during an endoscopic examination amounted to 86.0% and 72.0% respectively.[45]

Currently, the cut-off level of 50.0µg is considered an indicator of remission, while the value of 250.0µg is an indicator of the inflammation activity.[20] Other biochemical parameters, such as complete blood count (hemoglobin, platelets) and iron level, did not correlate with the disease activity, and therefore were not included in the analysis.

In imaging examinations, the usefulness of such techniques as ileocolonoscopy or MR enterography was analyzed. The most sensitive and specific method of assessing the activity of inflammation is ileocolonoscopy. Its limitation, however, is the scope of the examination since it only reaches the distal segment of the ileum. A dedicated scoring system for Crohn's disease, SES-CD, was introduced, so that ileocolonoscopy, as a method of assessing CD activity, could be reproducible and comparable. SES-CD is a scoring system based on a 0-3 scale, in which several variables are analyzed with reference to 5 bowel segments: ulceration, size of ulcers, affected surface of the intestine and presence of stenosis.[34]

In our study, SES-CD was used to assess the inflammation activity during ileocolonoscopy, with cut-off values <2.0 points – as an indicator of the disease inactivity – and >2.0 points – as an indicator of the disease activity. The sensitivity of this method was calculated at 93.6%, whereas the specificity – at 100.0%. PPV and NPV were 100.0% and 66.7% respectively. The accuracy was estimated at 94.6%. When using this method for the distal segment of the ileum, the sensitivity and specificity were 55.0% and 100.0% respectively, whereas PPV and NPV – 100.0% and 64.0%. The accuracy of the method in this case was 75.0%. Obviously, the values are different for the large intestine, where the sensitivity and specificity amounted to 96.4% and 100.0% respectively, with PPV and NPV of 100.0% and 90.0%. The accuracy was calculated at 97.3%. Thus, colonoscopy remains the gold standard when diagnosing IBD.[46]

When assessing the disease activity using a different imaging technique, i.e. MR enterography, the sensitivity of this diagnostic tool was 51.5%, whereas the specificity – 100.0%. PPV and NPV were 100.0% and 20.0% respectively. The accuracy stood at 56.8%. The sensitivity and specificity of MRE was slightly better for the small intestine: the values were 66.7% and 100.0% respectively, with PPV and NPV of 100.0% and 69.6%. The accuracy was 81.1%. For the large intestine, on the other hand, the sensitivity and specificity were significantly lower: 33.3% and 100.0% respectively, with PPV and NPV of 100.0% and 33.3%. The accuracy of this method for the large intestine was calculated at 50.0%.

Generally, it is thought that MRE, used as a tool for assessing CD activity, shows an average sensitivity and high specificity within the large intestine.[47] In a study by Maccioni et al.,[48] the sensitivity and specificity were calculated at 100.0% in the ileum. In other studies, where CTE and MRE were compared, the values stood at 89.0% vs. 83.0% for the sensitivity and 80.0% vs. 100.0% for the specificity.[47] It seems that MRE is a more sensitive diagnostic tool when detecting complications of the disease, such as fistulae or stenosis.[49]

All diagnostic tools analyzed above were also compared to each other, using a non-adjusted coefficient of agreement and the Cohen's Kappa coefficient. The comparison showed a strong correlation between an endoscopic examination – colonoscopy – and fecal calprotectin. In our study, the endoscopic accuracy was calculated at 77.1%, with a FC cut-off point of 43.0µg/g. If the process was in the large intestine, the cut off point for calprotectin was 100.0µg / g in 96.4% of cases. Similarly to other examinations,[50] where the accuracy of detecting an active inflammation process using endoscopy was 87.0% for the FC level of 70.0µg/g. This once again emphasizes that applying fecal calprotectin as a biomarker is an effective method of monitoring the inflammation process and may be used to optimize the therapeutic process.

Conclusion

a. By analyzing diagnostic methods used to assess the disease activity, both within the small intestine (the distal segment of the ileum) and the large intestine, it was found that Endoscopy is the most accurate diagnostic tool, followed by Fecal calprotectin. The least sensitive methods include: MR Enterography and CDAI.

b. A statistically significant agreement between Endoscopy and Fecal calprotectin was demonstrated.

The cut-off value of FC (taking into account both the small intestine and the large intestine), in correlation with endoscopic findings indicative of the disease activity, was 43.0µg/g.

The cut-off value of FC, in correlation with endoscopic findings indicative of the disease activity, was 100.0µg/g for the large intestine.

C-reactive protein (CRP) shows a statistical significance with CDAI and it correlated with the endoscopic appearance of the large intestine, MRE of the small intestine and the fecal calprotectin level.

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By assessing the inflammation activity for the small and large intestine separately, it was found that MRE is a slightly better diagnostic tool in the case of the small intestine, whereas ileocolonoscopy is a preferred method for examining the large intestine.

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Conflict of Interest

The author declares no conflict of interest.

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