

ORIGINAL PAPERS

Fecal calprotectin and C-reactive protein are associated with positive findings in capsule endoscopy in suspected small bowel Crohn's disease

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ABSTRACT

Background and aims: Capsule endoscopy is an extended tool for the diagnosis of small bowel Crohn's disease. However, factors associated with positive findings of this technique have not been well established. Our aim is to assess which factors are associated with a better diagnostic yield of capsule endoscopy in suspected small bowel Crohn's disease.

Material and methods: This was a retrospective study including patients under capsule endoscopy because of suspected small bowel Crohn's disease. Demographic data of these patients, as well as symptoms and laboratory data including hemoglobin levels, count of leucocytes and platelets, and levels of C-reactive protein, erythrocyte sedimentation rate and fecal calprotectin were collected. Capsule endoscopy studies were classified as negative (no lesions) or positive (lesions suggestive of Crohn's disease). Descriptive, univariate and multivariate analysis were done, as well as diagnostic yield tests of the different markers for predicting lesions in capsule studies.

Results: One hundred and twenty-four patients were included (85 women and 39 men). The average age was 38.21 years. Levels of C-reactive protein and fecal calprotectin were the markers more frequently associated with positive findings in capsule endoscopy. Calprotectin presented the best sensitivity as isolated marker. The association of altered levels of C-reactive protein and calprotectin showed the best specificity and predictive values.

Conclusions: C-reactive protein and fecal calprotectin are appropriate biomarkers for selecting patients with suspected Crohn's disease of the small bowel for capsule endoscopy studies.

Key words: Crohn's disease. Small bowel. Capsule endoscopy.

INTRODUCTION

Capsule endoscopy (CE) is an extended tool for the diagnosis of small bowel (SB) diseases. The main indications for this modality are obscure gastrointestinal bleeding or middle gastrointestinal bleeding (MGIB) and inflammatory bowel disease (IBD). In the most recent guidelines

by the European Society of Gastrointestinal Endoscopy (ESGE) (1), CE is recommended as the first-line investigation in cases of MGIB, and after a normal ileocolonoscopy in cases of suspected Crohn's disease (CD).

CE has shown a great diagnostic yield in MGIB (2), especially in individuals presenting with overt bleeding (3). Several authors have defined the factors associated with a higher rate of positive findings in CE studies in cases of MGIB (4,5), including male sex, age over 60 years, high number of pre-capsule endoscopic procedures, need for transfusions, patients with connective tissue or renal diseases, antiplatelet or nonsteroidal anti-inflammatory drugs intake, etc. However, although CE is an extended diagnostic tool in cases of suspected small bowel CD (SB-CD) (6), there are not definite data about the factors associated with the higher diagnostic yield of CE in this indication. We only found in the literature a few case series analyzing the association between symptoms or altered laboratory tests (a single symptom or test in most cases) and positive findings in CE studies in patients with suspected SB-CD (7,8). Therefore, no specific recommendations can be done about which patients can benefit the most from the technique in this specific indication.

OBJECTIVE

The aim of our study is to assess the association of different factors (including demographic data, symptoms and laboratory markers) with the presence of inflammatory lesions seen in CE studies of patients with suspected SB-CD. Furthermore, the characteristics of the patients who can benefit the most from this technique will be defined.

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METHODS

Study design and patient selection

This is a retrospective, single-center study in which demographic, clinical and laboratory data of patients under CE have been collected. Patients in which the indication for CE was suspected SB-CD were selected from our database. These patients presented chronic/recurrent diarrhea and/or abdominal pain. Suspicion of CD was also based on altered biochemical markers including anemia, leukocytosis, thrombocytosis and elevated levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fecal calprotectin (FC).

In all patients a previous lower endoscopy had been carried out with no findings, but only in 38% of cases a normal ileoscopy was also referred in the endoscopy report. In some cases, and depending on the patients' clinical situation, upper endoscopy or radiologic explorations were performed, being normal as well.

CE procedure

All CE studies were performed using the PillCam SB2 (from March 2012 to November 2012) and SB3 (Medtronic, formerly Given Imaging Ltd.). Rapid® software was used for processing and reading the videos.

For bowel preparation, patients were asked to keep a low-fiber diet some days prior to the procedure and fasting from the night before. Only in selected cases (elderly or bedridden patients, previous difficult bowel preparation for colonoscopy or CE, etc.) the patients received low doses of polyethylene-glycol.

CE studies have been reviewed and reported by one out of two experienced endoscopists in our unit. These were provided with clinical information about the patients (including demographic data, symptoms and laboratory data) when reading the videos.

Classification of CE findings

Diagnosis of lesions suggestive of SB-CD, as described in the literature (9), was based on the observation of villous edema and erythema, mucosal denudation, erosive lesions as aphthae or ulcers, and the presence of stenosis (Figs. 1 and 2). When any of these inflammatory lesions were seen we used the Lewis Score (LS) to assess severity: normal mucosa or non-significant inflammation, LS < 135; mild-moderate inflammation, LS: 135-790; severe mucosal affection, LS > 790 (10,11).

CE studies were initially classified into three groups: normal examinations (no lesions), non-significant studies, and CE presenting lesions suggestive of SB-CD. In the "non-significant" group we included those with non-inflammatory lesions (usually incidental findings) such as angioectasia or polyps, or studies with minimal inflammatory lesions such as isolated small aphtha, mild mucosal erosion or denudation, limited areas with mild edema or erythema, etc.; in conclusion, findings not related to IBD or insufficient for a diagnosis of CD, with LS < 135 (12). For statistical analysis normal and non-significant studies were included as negative CE, and those with significant inflammatory lesions and LS > 135 were considered to be positive CE.

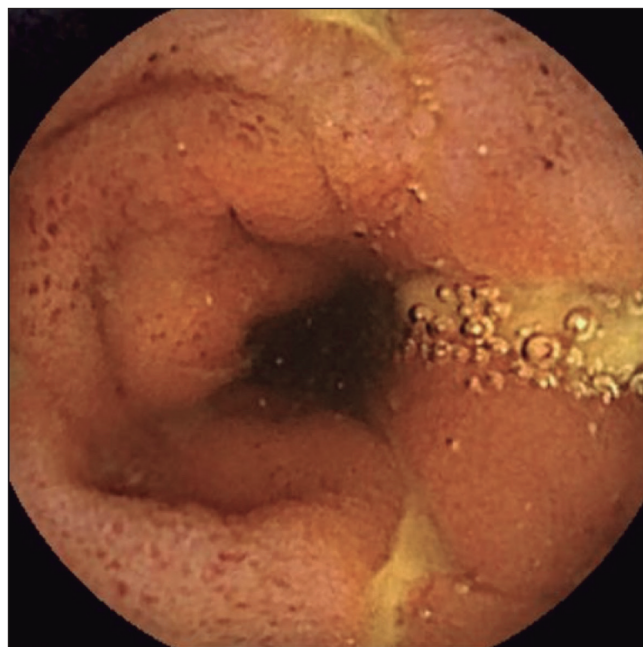


Fig. 1. Edematous mucosa showing petechiae and ulcers.

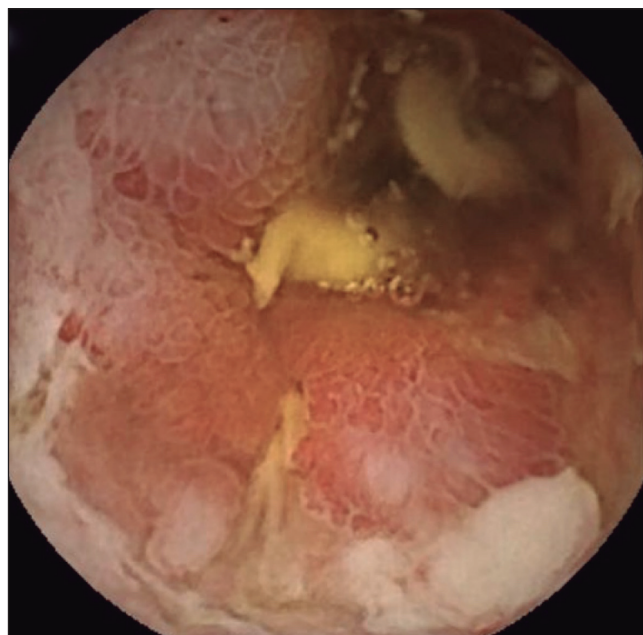


Fig. 2. Villous edema associated with an extensive ulceration and stenosis.

Clinical and laboratory data

Data from the patients' medical records were collected, including demographic data, symptoms and laboratory tests. The mean time between these determinations and performance of the CE studies was 73 days.

- *Symptoms:* we searched in all the medical records and included in the database the main symptom of every patient as

“diarrhea”, “abdominal pain” or “both” when none of them was predominant.

- *Hemoglobin levels*: we considered that a patient presented anemia when hemoglobin levels were lower than 12 g/dl in women and lower than 13.5 g/dl in men.
- *Leucocytes*: a patient presented leukocytosis if the white blood cell count was higher than 11,000/ μ L.
- *Platelets*: thrombocytosis was considered when platelets count was over 350,000/ μ L.
- *ESR*: this marker was altered when levels were higher than 20 mm/h.
- *CRP*: this parameter was considered as abnormal when levels were over 0.5 mg/dl.
- *FC*: in our center, levels of FC are determined by automated enzyme immunoassay analyzer (estimated sensitivity of 95%). The reference level for this marker in most cases is 50 μ g/g but some authors have reported that the diagnostic yield of FC in SB-CD improves when this cut-off is higher (13), and this was also one of the conclusions of a previous study of our group (8). Based on this evidence, in the present study FC > 100 μ g/g was considered as pathological level.

Statistical analysis

All statistical analyses were performed with IBM SPSSv19.0 (SPSS, IBM Company[®]) and STATA v10 (STATA[®], College Station, Texas). First, a descriptive analysis of the variables was made. Frequency of the qualitative variables was calculated and continuous data were reported as mean with its standard deviation. Laboratory data were expressed as continuous variables or dichotomic (normal test/abnormal test) when needed. Normal distribution was tested using the Kolmogorov-Smirnov test.

For univariate analysis the Chi-squared test and the Fisher’s exact test were used to compare categorical variables. When significant differences were found in laboratory data (normal test/abnormal test) the Student’s t test was performed for comparison of means. ANOVA test was used to analyze the mean differences of age among variables with more than two categories.

Multivariate logistic regression analysis was made including odds ratio (OR) of the variables.

Finally, sensitivity (SE), specificity (SP), negative predictive value (NPV), positive predictive value (PPV) and area under the curve (AUC) of the variables and the association of some of them were calculated.

In all cases a 95% confidence interval (CI) was used, and $p < 0.05$ was considered to be significant.

RESULTS

In a period of 38 months we found in our database that in 151 patients out of 439 the indication for CE was suspected SB-CD. Twenty-seven of them were excluded: 15 because data were incomplete or impossible to find, and 12 patients were taking non-steroidal anti-inflammatory drugs in the six weeks prior to CE. Finally, 124 individuals were included in the study.

The mean age of the patients was 38.21 years ($4-83 \pm 17.107$), 36.46 years ($4-83 \pm 17.852$) in men and 39.01 ($8-83 \pm 16.588$) in women. We found inflammatory lesions suggestive of CD in 43 cases (34.1%). There was no difference in the rate of positive CE between genders (36% in men and 34% in women). Frequencies of the different variables are shown in table I, and all of them have normal distribution.

Univariate analysis

When we analyzed the possible association of each variable with positive findings in CE we found no differences between genders ($p = 0.574$) or symptoms ($p = 0.298$). No differences were observed in the mean age of patients either with positive or negative CE (36.79 years ± 15.702 vs 38.81 years ± 17.907 ; $p = 0.536$).

No significant differences were found in the rate of positive CE between patients with anemia and patients with normal hemoglobin levels ($p = 0.206$), between patients with leukocytosis and normal leucocytes count ($p = 0.073$), or between patients with altered or normal levels of ESR ($p = 0.373$).

We found statistically significant differences between patients with thrombocytosis and those with normal plate-

Table I. Frequency table including all the variables except age

Variable	n	%	Positive CE
Sex: male	39	31.5%	14 (36%)
Sex: female	85	68.5%	29 (34%)
Symptom: diarrhea	45	36.3%	13 (29%)
Symptom: abdominal pain	50	40.3%	21 (42%)
Symptom: both	29	23.4%	9 (31%)
Normal Hb levels	102	82.3%	32 (31%)
Anemia	22	17.7%	11 (50%)
Normal leucocytes count	110	88.7%	35 (32%)
Leukocytosis	14	11.3%	8 (57%)
Normal platelets count	104	83.9%	32 (31%)
Thrombocytosis	20	16.1%	11 (55%)
Normal ESR	86	69.4%	30 (35%)
High levels of ESR	38	30.6%	21 (55%)
Normal CRP	87	70.2%	22 (25%)
High levels of CRP	35	29.8%	21 (60%)
Normal FC	72	58.1%	24 (33%)
High levels of FC	52	41.9%	32 (62%)
Total	124	100%	43 (34.1%)

N: Number of patients out of 124; %: Percentage out of 124.

lets count ($p = 0.041$). There were also significant differences when comparing the mean platelets count of patients with positive or negative CE ($310,523.81$ platelets/ $\mu\text{L} \pm 108,556.659$ vs $272,024.69$ platelets/ $\mu\text{L} \pm 63,001.979$; $p = 0.038$). However both means are in normal ranges for this marker (platelets $< 350,000/\mu\text{L}$), so clinical significance of this result is questionable.

Finally, significant differences were also observed between patients with normal or altered CRP ($p < 0.001$), and between patients with FC $< 100 \mu\text{g/g}$ and FC $> 100 \mu\text{g/g}$ ($p < 0.001$).

Multivariate analysis

The results of this analysis are summarized in table II.

We have found that patients with CRP > 0.5 mg/dl are more likely to present positive CE than those with normal levels of CRP ($p = 0.02$; OR: 6 [1.41-25.53]; CI: 95%). Patients with FC $> 100 \mu\text{g/g}$ are also at a higher risk of presenting positive findings in CE than those with FC $< 100 \mu\text{g/g}$ ($p < 0.001$; OR: 10.70 [3.54-32.33]; CI: 95%). In this analysis no significant differences were found for any of the other variables.

Diagnostic yield

We calculated SE, SP, predictive values and AUC for each biomarker and the association of CRP and FC with the rest of parameters. The main results of this analysis are included in tables III and IV.

Most of the biomarkers showed good SP (79-92.6%), being FC the less specific (SP: 76.5%). However, FC was

Table II. Multivariate logistic regression analysis of the association between the demographic, clinical and laboratory data and positive findings in VCE examinations

	Odds ratio	CI (95%)	p
Sex: male	1.24	0.42-3.70	0.70
Age	0.99	0.96-1.03	0.73
Symptom: abdominal pain	1		-
Symptom: diarrhea	0.58	0.17-1.92	0.37
Symptom: both	0.58	0.16-2.11	0.41
Anemia	2.39	0.48-11.86	0.29
Leukocytosis	1.85	0.28-12.28	0.52
Thrombocytosis	2.97	0.71-12.38	0.14
ESR > 22 mm/h	0.34	0.08-1.51	0.16
CRP > 0.5 mg/dl	6.00	1.41-25.53	0.02
FC $> 100 \mu\text{g/g}$	10.70	3.54-32.33	$p < 0.001$

CI: 95%.

the most sensitive parameter (SE: 76.7%) and presented the best NPV (84.2%), while the rest of markers had lower SE and NPV.

SP of FC improved in a very striking way when associated with any other altered laboratory test or with any of the symptoms. PPV of FC also showed better results in association with all the other biomarkers except ESR.

SP of CRP also improved in association with any other marker, but SE, NPV and PPV remained similar.

The best association of biomarkers was CRP plus FC (SP: 95.1%, NPV: 76.2%, and PPV: 82.6%).

When calculating AUC we found again the best results in CRP (0.693), FC (0.766) and the association of both (0.697). The rest of biomarkers and associations of biomarkers presented AUC: 0.546-0.593.

Complications

We registered four capsule retentions in patients with unknown or non-suspected stenosis in CD with severe affection of the SB. In all of them steroids were initialized, with good response and excretion of the capsule in two cases. The other two patients needed elective surgery as they presented complex stenosis, but the retention of the capsule did not condition the timing of surgery.

DISCUSSION

We have observed in our series that CRP and FC were the only biomarkers independently associated with the presence of inflammatory lesions suggestive of SB-CD in CE. These parameters also had the best results in terms of diagnostic yield.

The most common form of CD is ileocolonic, but it has been reported that in half of the patients with ileocolonic CD, lesions may also occur in other segments of the SB (14). On the other hand, up to one third of patients with CD may present with involvement of the SB alone and, in these cases, symptoms are more unspecific and diagnosis is more complex (15). Moreover, affection of the proximal SB has been associated with younger patients, higher rates of stenosis and higher need for surgery (16). This is why early and accurate diagnosis of SB-CD is important. CE is a useful and extended tool in this setting, and has shown to be superior to other diagnostic modalities (17,18).

Several guidelines and consensus documents by different organizations such as the European Society of Gastrointestinal Endoscopy (ESGE), the European Crohn's and Colitis Organisation (ECCO) and the American Society of Gastrointestinal Endoscopy (ASGE) have recommended CE in patients with suspected CD after a negative ileocolonoscopy and in absence of obstructive symptoms (1,19-22). In 2005, during the International Conference on Capsule Endoscopy (ICCE), it was established in a consensus

Table III. Sensitivity, specificity, predictive values and area under the curve of all the single laboratory tests and the association of CRP and FC

Variable	Sensitivity	Specificity	Negative PV	Positive PV	AUC
Anemia	25.6% (14.9-40.2%)	86.4% (77.3-92.2%)	68.6% (59.1-76.8%)	50% (30.7-69.3%)	0.560 (0.489-0.631)
Leukocytosis	18.6% (9.7-32.6%)	92.6% (84.8-96.5%)	68.2% (59-76.1%)	57.1% (32.6-78.6%)	0.556 (0.485-0.627)
Thrombocytosis	25.6% (14.9-40.2%)	88.9% (80.2-94%)	69.2% (59.8-77.3%)	55% (34.2-74.2%)	0.573 (0.501-0.644)
ESR > 20 mm/h	30.2% (18.6-45.1%)	79% (68.9-86.5%)	68.1% (58.1-76.6%)	43.3% (27.4-60.8%)	0.546 (0.474-0.618)
CRP > 0.5 mg/dl	55.8% (41.1-69.6%)	82.7% (73.1-89.4%)	77.9% (68.1-85.4%)	63.2% (47.3-76.6%)	0.693 (0.627-0.758)
FC > 100 µg/g	76.7% (62.3-89.2%)	76.5% (66.2-84.4%)	84.2% (72.1-92.5%)	60.8% (46.1-74.2%)	0.766 (0.706-0.826)
FC > 100 µg/g + CRP > 0.5 mg/dl	44.2% (30.4-58.9%)	95.1% (88-98.1%)	76.2% (67.1-83.5%)	82.6% (62.9-93%)	0.697 (0.631-0.762)

CI: 95%.

Table IV. Specificity, positive predictive value and area under the curve of the association of CRP or FC with any of the rest of biomarkers

	Specificity	Positive PV	AUC
FC > 100 µg/g + anemia	97.5% (91.4-99.3%)	77.8% (45.3-93.7%)	0.569 (0.497-0.641)
FC > 100 µg/g + leukocytosis	98.8% (93-99.8%)	87.5% (52.9-97.8%)	0.576 (0.504-0.647)
FC > 100 µg/g + thrombocytosis	100% (95.5-100%)	100% (67.6-100%)	0.593 (0.522-0.664)
FD > 100 µg/g + ESR > 20 mm/h	92.6% (84.8-96.5%)	62.5% (38.6-81.5%)	0.580 (0.508-0.651)
CRP > 0.5 mg/dl + anemia	97.5% (91.4-99.3%)	77.8% (45.3-93.7%)	0.569 (0.498-0.640)
CRP > 0.5 mg/dl + leukocytosis	95.1% (88-98.1%)	63.6% (35.4-84.8%)	0.557 (0.485-0.629)
CRP > 0.5 mg/dl + thrombocytosis	96.3% (89.7-98.7%)	70% (39.7-89.2%)	0.563 (0.491-0.635)
CRP > 0.5 mg/dl + ESR > 20 mm/h	87.7% (78.7-93.2%)	52.4% (32.4-71.7%)	0.567 (0.495-0.638)

CI: 95%.

document that suspicion of SB-CD should be based on the presence of clinical data (abdominal pain, diarrhea, weight loss, extra-intestinal conditions, etc.), altered biomarkers (anemia, leukocytosis, thrombocytosis, elevated levels of acute phase reactants, etc.) or abnormalities in imaging tests (23,24). In a study published in 2012, the authors showed that patients with these suspicion criteria were in fact more likely to present inflammatory lesions in CE, but they also reported that individuals with three or more of these criteria were at a significantly higher risk than those with only one or two of them (25). Based on these results in some systematic reviews about the role of CE in IBD, authors have indicated that the greater number of criteria a patient has, the higher the suspicion of CD should be, no matter which of the criteria are present (26,27). But it has not been completely analyzed if any of these criteria (or association of criteria) could be superior to the rest.

Some studies have been published trying to assess the association between symptoms (7,28) or isolated biomarkers with the presence of inflammatory lesions in CE. Regarding laboratory tests, we found some case series in the literature about the usefulness of fecal markers (most of them on FC), with heterogeneous and sometimes con-

flicting results (8,13,29,30). There are only a few short case series analyzing the association between symptoms and biomarkers together with findings in CE. In a series including 38 cases (31), the authors indicated that patients presenting with symptoms and altered biomarkers were more likely to present inflammatory lesions in SB than those only symptomatic. In one more case series including 23 patients (32) authors analyzed the possible association between different biomarkers and diagnosis of SB-CD in individuals with symptoms of the disease and prior negative study, concluding that patients with anemia and thrombocytosis were the best candidates for CE. In our series we found a statistically significant association between thrombocytosis and positive CE in univariate analysis, but this association was not confirmed in logistic regression analysis.

CE is related to high economic costs, both for the price of materials and equipment and the time-consuming work of the professionals involved, so it is important to make an accurate patient selection (33). There are many studies on this topic regarding cases of MGIB (3-5,34), and the characteristics of the patients who can benefit the most from the technique have been well defined in this indica-

tion, but not in cases of suspected SB-CD. CE has shown great NPV in IBD (35), being a good tool to rule out the disease, but the rate of positive CE in this indication in the literature is only between 26-52.4% (32,36,37). These data need to be improved, especially when compared to the rate of positive CE in cases of MGIB found in the literature, which is 47-84% (38-40).

As previously described (25), in our series we found that symptomatic patients who present two altered biomarkers (three ICCE suspicion criteria) have a significantly higher risk for presenting inflammatory lesions in CE. But our results go one step further as we observed that not all the associations of biomarkers mean an equivalent risk for the patients. When CRP or FC are one of the altered markers, the probability of finding lesions suggestive of CD of the SB is higher. Only these two variables were independently associated with positive findings in CE, and the association of both of them has the best results in terms of diagnostic yield. Among the other biomarkers only thrombocytosis has shown significant association with positive CE, but not independent and with a questionable clinical signification.

Limitations of our study are its retrospective nature and that patients come from one single center. More similar works are needed, including patients prospectively and from different reference centers if possible. Thus we shall be able to define more precisely the characteristics of the patients that may benefit the most from CE in this indication.

Our conclusion is that, among patients with IBD symptoms, those with at least two altered biomarkers including CRP and FC are the best candidates for CE. The probability of finding inflammatory lesions if only one biomarker is altered, or if there is an association of altered biomarkers excluding CRP or FC, is significantly lower.

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