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Lewis score: a useful tool for diagnosis and prognosis in Crohn's disease

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ABSTRACT

Background: videocapsule endoscopy (VCE) is currently the most sensitive diagnostic tool to detect early small bowel inflammation. A Lewis score (LS) of ≥ 135 as the cutoff value for the presence of significant inflammatory activity in patients undergoing VCE for suspected Crohn's disease (CD) has been suggested as a useful tool for the diagnosis of CD. The aim of this study was to evaluate the diagnostic and prognostic accuracy of the LS in patients with suspected CD undergoing VCE.

Methods: a retrospective single-center study was performed that included patients who underwent VCE for suspected CD between January 2010 and December 2015. Inflammatory activity was assessed with the LS. Patients were grouped according to the criteria of the International Conference on Capsule Endoscopy (ICCE) for the definition of suspected CD; group 1: patients not fulfilling ICCE and group 2: patients with ≥ 2 ICCE criteria.

Results: one hundred and ninety-one patients were included, 61% were female and the mean age was 39 ± 14 years. VCE detected significant inflammatory activity (LS ≥ 135) in 81 patients (42%); 24 patients from group 1 (32%) and 57 patients from group 2 (50%) (p = 0.014). During a mean follow-up period of 41 ± 21 months (12-79), a CD diagnosis was determined in 60 patients (31%); 55 patients with LS ≥ 135 (92%) and five patients with LS < 135 (5%) (p < 0.001). The LS showed a good diagnostic accuracy with an AUROC of 0.93 (p < 0.001). During the first year after diagnosis, there was a significant association between a higher LS and the need for immunomodulatory therapy, biological therapy, bowel resection surgery or hospital admission due to a CD flare-up.

Conclusions: the LS (cutoff ≥ 135) is very useful in the diagnosis of CD in patients undergoing VCE. Moreover, higher values of this score was associated with prognostic variables.

Keywords: Crohn's disease. Videocapsule endoscopy. Lewis score.

INTRODUCTION

Videocapsule endoscopy (VCE) has revolutionized small-bowel imaging by providing a noninvasive method for the complete assessment of the mucosa (1). This has led to an increase of its use for the evaluation of patients with known or clinically suspected Crohn's disease (CD) (2). VCE has a demonstrated superiority for the detection of small-bowel inflammatory lesions compared to ileocolonoscopy and imaging methods such as small-bowel follow-through, computed tomography (CT) or magnetic resonance (MRI) enterography (3).

Up to 66% of patients with CD have small-bowel involvement at diagnosis and the disease affects the terminal ileum in 90% of these cases. In this setting, ileocolonoscopy is the first-line investigative tool for suspected CD (1). However, CD frequently involves the proximal segments of the small-bowel, which are unreachable by ileocolonoscopy, and skipped lesions of the terminal ileum may result in false negative results. In this context, Rodrigues-Pinto et al. concluded that VCE was superior to cross sectional imaging for the detection of proximal lesions according to

data from their multicentric study. In fact, it could be a better examination in the setting of unexplained symptoms (4). In their study, 36% of cases had involvement of the proximal small-bowel in CD patients with ileal involvement, which was documented by ileocolonoscopy (4). However, based on the criteria that states that VCE should be performed only when ileoscopy is not possible or when lesions in the proximal small-bowel must be excluded, only 66% of these 36% patients would have undergone VCE (1,3). In this context, the International Conference on Capsule Endoscopy (ICCE) recommended that patients with suspected CD may be appropriate candidates for VCE, only if they present with typical symptoms in addition to either extraintestinal manifestations of CD, raised serological/hematological inflammatory markers, iron deficiency and/or abnormal small-bowel imaging findings (1).

The Lewis score (LS) is a cumulative scoring system that is based on the presence and distribution of villous edema, ulceration and stenosis along the small-bowel. The quantification of the inflammatory activity of the small-bowel in CD has been proposed (5,6). The LS aims to standardize the interpretation of lesions consistent with a diagnosis of CD and the quantification of inflammatory activity detected in the small-bowel mucosa. Thus, improving objectivity and inter-observer agreement (3,7).

Previous reports have shown that the application of LS ≥ 135 (equivalent to the presence of at least one small bowel ulcer) as the cutoff value for the presence of significant inflammatory activity in patients undergoing VCE for suspected CD may be useful to establish a diagnosis of CD (3). Nevertheless, the role of VCE in the management of patients with small-bowel CD is still evolving. The prognostic value of inflammatory activity in the follow-up of these patients is still unknown. Recently, some studies have investigated the role of VCE in the evaluation of CD prognosis and in therapy modifications. Furthermore, these studies reported that the grade of inflammatory activity quantified by the LS was a predictor of poor prognosis. In addition, there was a higher prevalence of corticosteroid therapy and hospitalization during follow-up in a cohort of CD patients of different stages, such as flare-up, clinical remission and postsurgical surveillance groups (6,8). As CD is a chronic complex disease involving several therapeutical interventions, these may influence the prognosis. Thus, the best assessment for the role of VCE in the clinical course of CD

would be at the time of diagnosis, before starting specific therapy.

The aims of this study were to evaluate the diagnostic accuracy of the LS in patients with suspected CD undergoing VCE and to evaluate the prognostic value of the severity of inflammatory lesions at diagnosis, quantified by the LS.

METHODS

A retrospective single-center study was performed of all consecutive patients undergoing VCE for suspected CD, between January 2010 and December 2015. All patients had a colonoscopy as the first endoscopic procedure, via ileoscopy in 85% of cases. The ileum was not intubated in the remaining cases due to the inability of the endoscopist or a poor right colon preparation that impeded an adequate visualization. Patients had to be free of non-steroidal anti-inflammatories (NSAIDs) for at least one month (1). Patients with endoscopic inflammatory lesions consistent with the diagnosis of CD at ileocolonoscopy were excluded.

Patients were grouped according to the criteria of the ICCE for the definition of suspected CD as follows: group 1: patients not fulfilling at least two ICCE criteria; and group 2: patients fulfilling at least two ICCE criteria. According to ICCE, CD was suspected if patients presented suggestive gastrointestinal symptoms (chronic abdominal pain, chronic diarrhea, weight loss and/or growth failure) plus either extraintestinal manifestations (fever, arthritis/arthralgias, pyoderma, perianal, primary sclerosing cholangitis), inflammatory markers (iron deficiency, erythrocyte sedimentation rate, leukocytosis, serology or fecal markers) or abnormal imaging studies (small-bowel series or CT scan) (1).

The patients with obstructive symptoms underwent VCE after confirming small-bowel patency using the Agile Patency capsule (Given®, Imaging Ltd. Yoqneam, Israel), which was assessed 30 hours after ingestion with a radiofrequency identification scanner. VCE was performed using PillCam® SB2 or SB3 capsules (Given®, Imaging Ltd.). Patients were instructed to follow a liquid diet on the day prior to the exam and 12 hours before the procedure a bowel preparation was performed with 1 liter of macrogol (polyethylene glycol 3350). During the procedure, the patients were kept on a clear-liquid diet.

All VCE videos were read by two experienced gastroenterologists (over 300 procedures) using the RAPID Reader® v.8.0. The software of the application was used to calculate the LS in all procedures (5). The LS was classified as normal or clinically insignificant if < 135 points, mild inflammatory activity if ≥ 135 and < 790 and moderate/severe inflammatory activity if ≥ 790. The grade of bowel preparation was evaluated according to the Aronchick scale.

The events considered to be CD complications that implied a worse outcome were: flare requiring systemic corticosteroid therapy, hospital admission, immunomodulatory and/or biologic therapy and surgery during follow-up.

Subsequent diagnosis of CD was established during the follow-up period (a minimum of 12 months after VCE exam), independently by the assistant physician. This was performed according to international guidelines based on a combination of clinical, endoscopic, histological, radiological and/or biochemical data. In the setting of CD diagnosis, these patients were additionally followed for at least 12 months after diagnosis.

Statistical analysis was performed using SPSS v. 24 (IBM®, Armonk, NY). Data was analyzed using the Chi-squared test for categorical variables, the t-test for independent-samples and the Mann-Whitney U nonparametric test for continuous variables. Multivariate analysis using binary logistic regression was performed using the variables selected from univariate analysis when $p \leq 0.1$ as predictors. Model discrimination was measured using the area under the receiver operating characteristic curve (AUROC), considering the 95% confidence intervals (CIs). Statistical significance was considered if the p-value was less than 0.05.

Ethical considerations

All patients provided written informed consent for VCE. The study was performed according to the Declaration of Helsinki. All rules of the local ethics committee (Comissão de Ética para a Saúde do Centro Hospitalar São João/Faculdade de Medicina da Universidade do Porto) were followed, preserving patient identity and confidentiality.

RESULTS

During the study period, 191 patients (61% female, mean age 39 ± 14 years) with suspected CD that fulfilled the inclusion criteria were analyzed. Patients were followed for a mean period of 41 ± 21 months (12-79) after the VCE exam. Changes in Ileocolonoscopy were found in 40% of patients, mainly non-specific inflammatory changes that were insufficient for a CD diagnosis. A previous small bowel study by imagiologic studies (enterography by CT or MRI) was performed in 34% of patients and lesions were found in 18% of cases. The demographic and clinical characteristics of the study population are shown in table 1.

With regard to the PillCam® capsule model used, 126 (66%) were SB2 and 65 (34%) were SB3 capsules. According to the Aronchick scale, 3% of patients had a poor bowel preparation. During the follow-up period, a CD diagnosis was established in 60 patients (31%), 46 in group 2 (40% had a CD diagnosis in this group) ($p < 0.001$).

The overall median LS was 0 (IQR 0-450) and significant inflammatory activity (LS ≥ 135) was detected in 81 patients (42%); 24 patients from group 1 (32%) and 57 patients from group 2 (50%) ($p = 0.014$). Among patients with CD, 55 had LS ≥ 135 (92%) and five patients had LS < 135 (8%) ($p < 0.001$). Overall, group 1 patients had a higher median LS compared to patients from group 2 ($p = 0.016$). The LS had a good diagnostic accuracy for CD with an AUROC of 0.93 ($p < 0.001$) (Fig. 1). Considering an LS cutoff of 135, this score had a sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of CD of 92%, 80%, 68% and 96%, respectively.

Patient demographic and clinical data are summarized in table 2, according to CD diagnosis during follow-up. In addition to the LS value, the presence of extraintestinal manifestations, lesions found by ileoscopy and a CRP level ≥ 3 mg/l at the time of the VCE examination were associated with CD diagnosis ($p = 0.039$; $p < 0.001$ and $p = 0.005$, respectively). Furthermore, an LS ≥ 135, the presence of extraintestinal manifestations and lesions found by ileoscopy remained independent predictors for a CD diagnosis, according to the multivariate analysis with an RR of 69.8 ($p < 0.001$; 95% CI 19.9-245.1), 4.8 ($p = 0.003$; 95% CI 1.7-13.6) and 6.2 ($p = 0.001$; 95% CI 2.1-18.9), respectively.

The characteristics of patients with a CD diagnosis according to the development of disease complications are described in table 3. During the first year after CD diagnosis, 28 (47%) patients had at least one disease flare that required systemic corticotherapy in four cases (7%), immunomodulatory in 27 (46%) or biological therapy in five (8%), hospitalization in two (3%) or surgery in two cases (3%) (Table 4). The development of complications was associated with higher levels of LS (675 [450-1,358], [p = 0.024]). Specifically, there was an increase in the indication for immunomodulatory therapy in individuals with higher LS values (675 [450-1,360] [p = 0.043]). However, when considering the cut-off previously defined for LS (≥ 135), although there are a greater number of complications in these patients, the difference between the medians of the groups was not statistically significant.

According to the univariate analysis, the presence of chronic diarrhea and CRP ≥ 3 mg/l were associated with the risk of a CD flare (p = 0.001 and p = 0.028, respectively). However, only the presence of chronic diarrhea was an independent risk factor for a flare according to the multivariate analysis, with an RR of 5.8 (p = 0.005; 95% CI 1.7-20.1). When assessing each adverse event separately, the presence of chronic diarrhea and CRP ≥ 3 were associated with the start of immunomodulatory therapy according to the univariate analysis (p = 0.003 and p = 0.034, respectively). A structuring/penetrating phenotype and the presence of perianal disease were associated with the need for corticotherapy (p = 0.002 and p = 0.002, respectively). According to the multivariate analysis, chronic diarrhea was independently associated with the start of immunomodulatory therapy, with a RR of 3.9 (p = 0.035; 95% CI 1.1-14.0). Furthermore, the presence of a structuring/penetrating phenotype was considered as an independent risk factor for corticotherapy, with an RR of 0.013 (p = 0.013; 95% CI 0.001-0.185). It was not possible to identify risk factors associated with the need for biologic therapy, hospitalization or surgery with statistical significance.

DISCUSSION

As described in the recent ECCO guidelines, there is no validated gold standard for the diagnosis of CD, which is based on an integration of clinical, biological, endoscopic, histologic and imaging data. VCE has a higher sensitivity to detect mucosal lesions

compared to conventional cross-sectional imaging modalities such as MRI enterography or CT enterography. In fact, VCE has a crucial role in CD diagnosis, particularly in patients with a high clinical suspicion and normal ileocolonoscopy and imaging (9), even though the exact VCE diagnostic criteria are undefined, as the lesions detected by this method are nonspecific. Differential diagnosis should be considered, with nonsteroidal anti-inflammatory drugs enteropathy.

The LS adds value to the VCE because it allows a standardized assessment of the grade of inflammatory activity, regardless of the etiology. In a recent study of 95 patients, Monteiro et al. concluded that LS had a high sensitivity and specificity to diagnose CD in patients with suspected disease, as defined by the ICCE criteria.

Our study represents the largest series in literature about this issue and included 191 patients. The aim was to evaluate the diagnostic and prognostic accuracy of VCE with LS, as a quantitative assessment of small-bowel inflammatory activity. We assumed the value of LS ≥ 135 as significant in bowel inflammatory activity, as it is more commonly used in the scientific literature (10). As described in table 2, a CD diagnosis was established in 92% of cases for patients with LS ≥ 135. In addition, the CD diagnosis was more frequent in the group with suspected CD according to the ICCE criteria (group 2) compared with group 1 (without ICCE criteria). When associating the ICCE criteria with the endoscopic criteria (LS ≥ 135), the specificity for CD diagnosis increased (80 to 89% with a decrease in sensitivity from 92 to 72%) due to the higher restriction of the combination of both criteria. All these results focus on the need for a careful clinical evaluation of each patient before VCE, as the CD diagnosis is more likely when ICCE criteria are present. Furthermore, the positive predictive value increased to 76% when both factors were combined.

We believe that for the purpose of a CD diagnosis, achieving a high sensitivity and negative predict value is of clinical importance, in order to accurately rule out patients without CD with a minimal false negative rate.

With regard to the prognostic significance of the inflammatory lesion severity assessed with LS, some studies (6,8) concluded that the prevalence of disease exacerbation was higher in patients with a LS ≥ 790. In these studies, disease exacerbation was defined as a disease flare that required systemic corticosteroid therapy, hospitalization or

surgery. In our study, a disease flare occurred in 51% of CD patients during the first year, which was defined as the need for systemic corticosteroid therapy, hospital admission, immunomodulatory or biologic therapy. In addition, we found that disease flare-up was associated with higher inflammatory activity, as evaluated by LS (675 [450-1,358], [p = 0.024]), thus demonstrating the prognostic value of this score, namely its ability to predict the severity of DC. For this study population, a cut-off of 440 in LS was related to the development of complications, with a sensitivity of 86% and a specificity of 39% (AUC of 66%, p = 0.033).

In the study of Veloso et al. (11), a younger age (< 40-year-old), ileocolonic disease and perianal disease at diagnosis were related to the risk of a CD flare. In our study, the presence of chronic diarrhea and higher PCR's values (≥ 3) at the time of diagnosis was predictive of disease severity, according to the logistical regression analysis. With regard to the disease behavior, our study demonstrated that patients with penetrating and/or structuring disease or perianal disease were more frequently treated with corticotherapy.

Our study has some limitations, mainly related to its retrospective design. In addition, the criteria for immunosuppression, biologics or patient admission may vary according to the assisting physician and patient preferences. This may have introduced a bias, as this recorded data was used to determine outcome.

In conclusion, the LS (cutoff ≥ 135) is very useful for the diagnosis of CD in patients undergoing VCE, with a high sensitivity and negative predictive value. VCE diagnostic accuracy may be improved by applying the ICCE criteria for the definition of suspected CD. Furthermore, this score has a prognostic value that allows us to predict which patients are most likely to have a clinically significant worsening of their disease during the first year after diagnosis.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1. Demographic and clinical characteristics of the study population

LS: Lewis score; CRP: C-reactive protein. Anemia: hemoglobin < 12 or < 13 g/dl (females or males, respectively). Iron deficiency: ferritin < 30 ng/ml.

	Group 1	Group 2	*p value*
No. patients (%)	76 (40)	115 (60)	
Male, n (%)	31 (42)	43 (58)	*0.652*
Age (mean ± SD [years])	39.9 ± 13.6	38.6 ± 13.4	*0.436*
LS (median [IQR])	0 (0-225)	112 (0-450)	*0.016*
LS ≥ 135, n (%)	24 (32)	57 (50)	*0.014*
LS ≥ 790, n (%)	5 (7)	18 (16)	*0.059*
CD confirmed diagnosis, n (%)	14 (18)	46 (40)	*0.001*
ICCE major criteria ≥ 2, n (%)	21 (28)	43 (37)	*0.162*
Perianal disease, n (%)	1 (1)	11 (9)	*0.115*
Extraintestinal manifestation, n (%)	5 (7)	29 (25)	*< 0.001*
CRP ≥ 3 mg/l, n (%)	1 (1)	85 (74)	*< 0.001*
Anemia, n (%)	3 (4)	17 (15)	*0.017*
Iron deficiency, n (%)	0 (0)	26 (23)	*< 0.001*

Table 2. Demographic and clinical characteristics of the population, according to CD diagnosis during follow-up

	Not confirmed CD	Confirmed CD	*p value*
No. patients (%)	131 (69)	60 (31)	
Male, n (%)	50 (38)	24 (40)	*0.873*
Age (mean ± SD [years])	39.6 ± 14.1	38.1 ± 11.9	*0.460*
Changes in ileoscopy, n (%)	33 (31)	35 (65)	*< 0.001*
LS ≥ 135, n (%)	26 (20)	55 (92)	*< 0.001*
LS ≥ 790, n (%)	0 (0)	23 (38)	*< 0.001*
ICCE major criteria ≥ 2, n (%)	39 (30)	25 (42)	*0.106*
LS ≥ 135 and ICCE group 2, n (%)	14 (11)	43 (72)	*< 0.001*
Perianal disease, n (%)	8 (6)	4 (7)	*0.904*
Extraintestinal manifestation, n (%)	20 (15)	17 (28)	*0.039*
CRP ≥ 3 mg/l, n (%)	50 (38)	36 (60)	*0.005*
Anemia, n (%)	12 (9)	8 (13)	*0.382*
Iron deficiency, n (%)	19 (15)	7 (12)	*0.596*

LS: Lewis score; CRP: C-reactive protein. Anemia: hemoglobin < 12 or < 13 g/dl (female or males, respectively). Iron deficiency: ferritin < 30 ng/ml.

Table 3. Characteristics of patients with a CD diagnosis, according to the development of disease complications

	Relapse	No relapse	*p value*
No. patients (%)	28 (51)	30 (49)	
Male, n (%)	10 (36)	12 (55)	*0.737*
Age (mean ± SD [years])	35.2 ± 10.6	40.9 ± 12.8	*0.075*
Changes in ileoscopy, n (%)	16 (60)	18 (72)	*0.335*
LS (median [IQR])	675 (450-1,360)	450 (225-908)	*0.024*
LS ≥ 135, n (%)	28 (100)	27 (83)	*0.054*
LS ≥ 790, n (%)	13 (46)	8 (30)	*0.018*
Perianal disease, n (%)	2 (7)	2 (7)	*0.135*
Extraintestinal manifestation, n (%)	5 (18)	11 (37)	*0.454*
Weight loss, n (%)	2 (7)	2 (7)	*0.009*
Abdominal pain, n (%)	17 (61)	16 (53)	*0.571*
Chronic diarrhea, n (%)	23 (83)	12 (40)	*0.001*
CRP ≥ 3 mg/l, n (%)	21 (75)	14 (47)	*0.028*
Anemia, n (%)	6 (21)	1 (3)	*0.106*
Iron deficiency, n (%)	5 (18)	1 (3)	*0.184*

LS: Lewis score; CRP: C-reactive protein. Anemia: hemoglobin < 12 or < 13 g/dl (females or males, respectively). Iron deficiency: ferritin < 30 ng/ml.

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Table 4. Specific disease complications

	Immunomodulator therapy	p value	Biological therapy	p value	Corticotherapy	p value	Hospitalization	p value
Patients, n (%)	27 (46)		5 (8)		4 (7)		2 (3)	
Male, n (%)	9 (33)	0.437	1 (20)	0.639	3 (75)	0.289	1 (50)	0.999
Age ≥ 40 y, n (%)	9 (33)	1.000	2 (40)	0.999	1 (25)	1.000	1 (50)	0.999
LS (median [IQR])	675 (450-1,360)	*0.043*	586 (225-1,358)	0.774	729 (248-3,035)	0.695	261 (135-/)	0.338
LS ≥ 135, n (%)	27 (84)	0.056	5 (100)	0.999	4 (100)	1.000	2 (100)	0.839
LS ≥ 790, n (%)	10 (31)	0.418	3 (60)	0.999	2 (50)	0.620	0 (0)	0.529
Disease behaviour								
Non-stricturing non-penetrating, n (%)	23 (85)	0.398	4 (80)	0.374	1 (25)	*0.002*	1 (50)	0.195
Stricturing/Penetrating, n (%)	4 (15)		1 (20)		3 (75)		1 (50)	
Disease location								
Ileum/colon	10 (37)	0.124	0 (0)	0.053	2 (50)	0.999	0 (0)	0.493
Ileocolon | + Upper GI location	17 (63)		5 (100)		2 (50)		2 (100)	
Perianal disease, n (%)	2 (7)	0.415	1 (20)	0.094	2 (50)	*0.002*	1 (50)	0.130
Extraintestinal manifestation, n (%)	10 (34)	0.273	1 (20)	0.916	3 (75)	0.977	1 (50)	0.798

LS: Lewis score; CRP: C-reactive protein. Anemia: hemoglobin < 12 or < 13 g/dl (women or men, respectively). Iron deficiency: ferritin < 30 ng/ml.

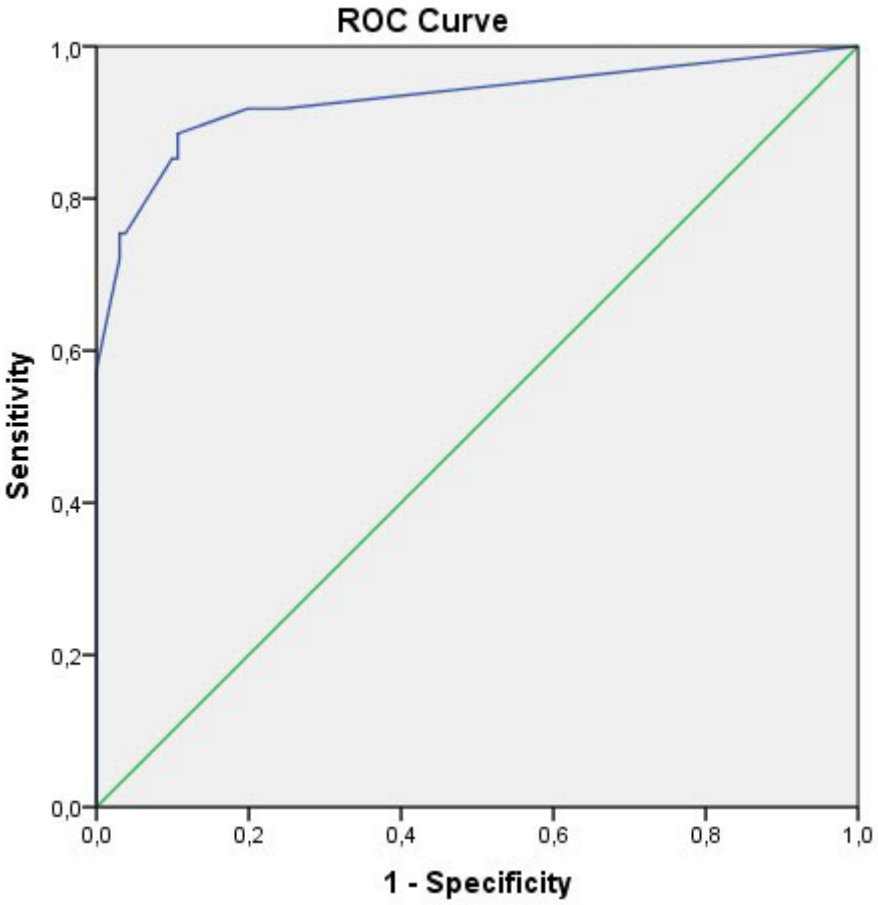

Fig. 1. ROC curve: accuracy of LS in the diagnosis of CD.