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A. Endoscopic visualization of the esophagogastric anastomosis' fistula.
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Impact of Continuing Education on Further Disseminating Knowledge of Inflammatory Bowel Disease

Fabio Leonel Gil-Parada^{1*}. 

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Given the increased prevalence of inflammatory bowel disease (IBD) in Colombia and Latin America, it is necessary to create mechanisms for disseminating knowledge of the disease, understanding its manifestation context, and diagnosing it on time for better outcomes^(1,2). IBD is a severe and disabling pathology that harms patients' quality of life, including their emotional, functional, social, work, and family spheres, despite the multiple therapies available.

The endeavors and publication of the Hospital Universitario Fundación Santa Fe de Bogotá Multidisciplinary Research Group, "Characteristics of Inflammatory Bowel Disease Compared to Other National Centers in Colombia," exemplarily illustrate the progress in knowledge of ulcerative colitis (UC) and Crohn's disease (CD), their clinical manifestations, and medical and surgical treatment. This national research diagnosed 386 patients for 23 years (1996–2019) in a referral center, where generally more complex patients with higher hospitalization and surgery rates attend.

The results of this relevant publication, which is also part of the national registry of Colombia⁽³⁾, show a predominance of UC, pancolitis in 42.6% of cases with an average age of 50 years, and a high percentage of severe disease (35.45%). In CD patients, location, involvement of the ileum, and stenosing behavior predominate in half of the cases. The cases of primary sclerosing cholangitis reflect great severity and the relationship with neoplasia as an associated risk factor.

Regarding IBD management in this group, most UC patients received salicylates (94%), steroids (57%), and azathioprine (30%). The application of biological therapies was low (13%) compared to 47.5% of CD patients. The percentage of colectomy (16.25%) in UC patients, with an average of 8.1 years from diagnosis to intervention, and the severity of the disease with resistance to medical management and complications may also reflect the context of a referral center. In CD patients, the indication for surgery was earlier, an average of four years from the diagnosis of the disease; 55.9% of the patients underwent surgery, the most frequent cause being an intestinal obstruction followed by perianal disease.

Information management in databases and multidisciplinary participation in the Fundación Santa Fe encourage all institutions to channel medical records—considering the implications for IBD patients due to their risk factors—, history of vaccination, infections, comorbidities, specific diagnostic criteria, objective severity assessment scales, disease activity, and evaluation of outcomes reported by patients, following natio-

nal, European, American, and international organization guidelines to study IBD, among others⁽⁴⁾.

Despite the dedication to and knowledge of this pathology, there are still many matters to analyze and improve. For example, how to mitigate the COVID-19 pandemic's impact on the follow-up of patients due to the risk of relapse. We should delve into strategies to understand better the pathophysiological role of genetic susceptibility and the intestinal microbiome, improve phenotyping, nutrition, physical activity, monitor medication levels and antibodies to guide therapies, and spread knowledge to promote deep and sustained remission and mucosal and histological healing. Because of the impact of the disease on patients' quality of life and psyche, it is imperative to devise strategies to benefit the patient's emotional health.

With the ongoing work of the board of directors of the Colombian Association of Gastroenterology and the Colombian Crohn's and Colitis Study Group (GECCOL),

this is an invitation to go to the association's website and social media, such as YouTube, and see the history of IBD with quality and constantly updated information.

This information can be disseminated in your workgroups hoping to reach the front doors of the emergency rooms or primary care consultations, where most potential patients go. Continuing education for health workers is important to make them aware of timely diagnosis and specialized management of situations that can become very complex, even for expert hands, and continue improving the quality of care.

The Colombian Association of Gastroenterology runs the project to support and certify centers of excellence for IBD patients' care with the support of the Pan American Crohn's and Colitis Organization (PANCCO) and the Spanish Group of Work on Crohn's Disease and Ulcerative Colitis (GETECCU) to provide adequate quality of care and improve outcomes for patients⁽⁵⁾.

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Severity Markers of Acute Appendicitis: Diagnostic Test Study

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Abstract

Introduction: Acute appendicitis (AA) is one of the most frequent abdominal surgical pathologies globally, with appendectomy being the most performed emergency surgery. **Aim:** To determine potential markers of AA severity for diagnostic purposes and timely management, thus avoiding possible complications. **Materials and methods:** This research relies on a randomized sample of 239 patients diagnosed with AA at the Orinoquía Regional Hospital, Colombia. We analyzed blood count, C-reactive protein (CRP), and neutrophil/lymphocyte ratio (NLR) records and established their relationship with the AA surgical findings described by Guzmán-Valdivia. **Results:** In the emergency department, these reactants can provide an approximate diagnosis as markers of the AA severity, with CRP > 15 mg/dL (diagnostic accuracy of 76.15 %) and NLR > 85 % (diagnostic accuracy of 61.09 %) having the best initial operating performance. Regarding complications such as intestinal perforation, we found a statistical relationship; CRP > 15 mg/dL and NLR > 85 % were the markers with the highest predictive performance, with OR 14.46 and OR 2.17, respectively, regarding Guzmán-Valdivia's findings. **Conclusions:** CRP and NLR > 85 % are the acute phase reactants with the best diagnostic characteristics to predict potential AA complications.

Keywords

Appendicitis, perforation, biomarkers, severity.

INTRODUCTION

Appendicitis is defined as inflammation of the vermiform appendix, the most common cause of acute abdomen (approximately 60%). Thus, appendectomy is the most performed emergency surgery worldwide⁽¹⁻⁴⁾. It has been estimated that the risk of having this disease throughout life is approximately 12%^(2,3,5), with young people under 29 years of age making up 45% of patients^(4,6-9).

This pathology occurs due to inflammation of the cecal appendix, secondary to the obstruction of its lumen by fecal

liths, lymphoid hyperplasia, tumors, parasites, among others. It disrupts local blood flow, irritating the adjacent peritoneum and causing pain. Finally, it results in a perforation of the anatomical structure, releasing intestinal content into the abdominal cavity and causing complications, such as peritonitis, sepsis, shock, and, in some cases, death⁽¹⁰⁻¹²⁾. The clinical picture must be known and the pathology identified in time to avoid this. However, there is a great variety of manifestations among individuals, age groups, and genders. There are also several differential diagnoses to consider, leading to a wrong or late diagnosis in one out of five patients⁽¹³⁻¹⁷⁾.

To make a timely diagnosis and reduce the rate of complications in patients with appendiceal pathology, the clinical component must be considered, together with diagnostic tests (paraclinical tests). They can reduce the error from an estimated 22% to 5%, representing a cost reduction of up to 200,000 euros per year⁽¹⁸⁾. Numerous scales have been developed to help the clinician recognize which patients with abdominal pain are more likely to have the disease. The available scales include the Alvarado score, the pediatric appendicitis score (PAS), and the RIPASA score, which assign scores to clinical manifestations and incorporate laboratory test results⁽¹⁸⁻²¹⁾. However, there is no biomarker with optimal performance that effectively diagnoses acute appendicitis (AA) or can predict its severity or complications⁽¹⁹⁻²¹⁾.

This article aims to analyze the potential markers of severity in AA for diagnostic purposes and timely management of surgical diseases in emergency services.

MATERIALS AND METHODS

Population

The study group comprised the entire population with a diagnosis of AA treated at the Hospital Regional de la Orinoquía (HORO) in Yopal between January 1, 2013, and December 31, 2018. It will be identified using the international code of diseases (ICD-10) as follows: K37 (Unspecified appendicitis); K35.9 (Acute catarrhal, fulminant, gangrenous, obstructive, retrocecal, and suppurative appendicitis); K35.1 (Acute appendicitis with peritoneal abscess); K35.0 (Acute appendicitis, perforation, peritonitis, or rupture); A06.8 (Amoebic appendicitis); and K36 (Obstructive appendicitis).

To calculate the sample, the following variables were considered: The population served according to the institution's clinical records was 760 people diagnosed with appendicitis, the prevalence of appendicitis of 24.6%⁽²²⁾, the margin of error of 5% and 95% confidence interval (95% CI). As a result, 239 people were included in the study, who were selected by simple random probabilistic sampling.

Inclusion criteria

The population treated at the HORO from 2013 to 2018 with an Alvarado score⁽²²⁾ was included. A score of 5 to 6 is compatible with the diagnosis of AA; 7 to 8 indicates probable appendicitis; and 9 to 10 indicates a very probable appendicitis, together with imaging (ultrasound or tomography) and histopathological studies to confirm the diagnosis. In addition, the Guzmán-Valdivia scale was considered according to the intraoperative findings.

Exclusion criteria

We excluded medical records with incomplete or nonexistent blood count (BC), C-reactive protein (CRP), neutrophil/leukocyte ratio (NLR), and minors (18 years) from the study.

Variables

Based on Calvo *et al*'s study⁽²³⁾, a list of variables was established, including sociodemographic (sex, age, rural or urban origin), clinical (acute pain in the epigastrium radiating to the right iliac fossa, fever) and paraclinical (leukocyte count >11,000, neutrophil percentage > 85%, lymphocyte percentage > 10%, NLR > 5.5, and CRP > 15 mg/dL) data.

Statistical analysis

The database was registered in Excel, version 2013, and analyzed in the statistical package SPSS, version 22. The univariate analysis was performed using a descriptive statistic for the selected population, and the absolute and relative frequencies of the categorical variables were determined. In the case of quantitative variables, we calculated measures of central tendency (mean, median) and dispersion (standard deviation and interquartile range) according to the distribution of the variable.

The cut-off value for leukocyte count (> 11,000/mm³), neutrophil percentage (> 85%), lymphocyte percentage (> 10%), CRP (> 15 mg/dL), and NLR (> 5.5) were determined using ROC curves (receiver operating characteristics) using SPSS software, version 22, to differentiate severe from uncomplicated cases. Finally, to determine the possible associations between the categorical variables, tetra-choric tables were made with diagnostic Odds Ratio measurement and their respective 95% CI (< 1 as a predictor of mild (without perforation); > 1 as a predictor of severe (perforation); and one without association). Additionally, we estimated the operating characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) of the paraclinical tests performed more frequently during the hospitalization of patients with AA.

Biases

The risk of bias is deemed low since the scale used as the reference method (Guzmán-Valdivia) is based on the findings during the surgical procedure. These findings are classified into four grades (0: No appendicitis (prophylactic appendicitis, no post-surgical antimicrobial scheme); Ia: Edematous and engorged, Ib: Abscessed or phlegmo-

nous (with seropurulent fluid around the appendix), Ic: Necrotic without perforation; II: Perforated with localized abscess; III: Complicated appendicitis with generalized peritonitis). It maintains a low risk of error and the dichotomization to assess severity. In the case of the qualitative variables, they were taken as dichotomous to analyze and adequately calculate the operating characteristics, which facilitated the assessment and grouping of the participants.

Ethical considerations

Based on Resolution 8430/1993, the study was considered riskless since it was based on the review of medical records. Additionally, we requested the proper permits from the institution keeping the records.

RESULTS

Two hundred thirty-nine medical records of patients diagnosed with AA were evaluated (**Figure 1**).

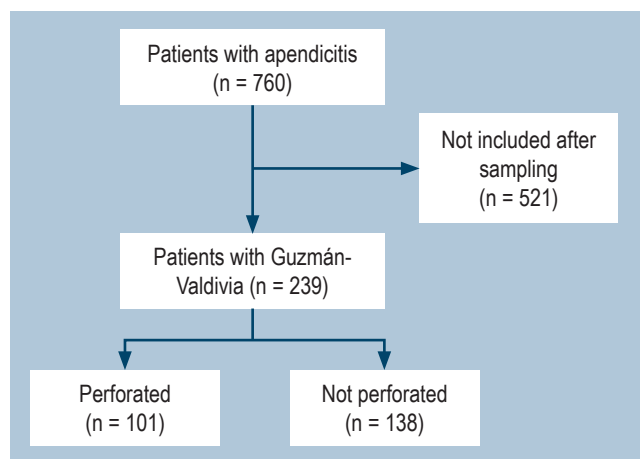


Figure 1. Process for obtaining and selecting patients according to sample size

Sociodemographic characterization

The population's average age was 26.35 years, with an SD \pm 6.4 years (coefficient of variation of 24%), ranging from 18 to 46 years. **Table 1** shows the characteristics of the population.

Regarding the characteristics of inflammatory reactants, we observed that the mean value of the leukocyte count was 15,512.2/mm³, with an SD \pm 5,386.84/mm³ (minimum of 1,904.1/mm³; maximum of 32,000/mm³). The percentage of neutrophils had a mean value of 12.625, with an SD \pm 5,338.36/mm³ (minimum of 1,294.72/mm³; maximum of 27,840/mm³). The lymphocytes had a mean value of 2,271.28/mm³, with an SD \pm 2,125.6/mm³ (minimum of 443/mm³; maximum of 17,908/mm³).

Table 1. Population characteristics

Variable	N	%	95% CI	
Sex				
- Female	127	53	46.81	59.46
- Male	112	47	40.54	53.19
Residence				
- Urban	155	64.8536	65.21	79.31
- Rural	84	35.1464	29.09	41.2
Grade according to the Guzmán-Valdivia scale				
- 1a	65	27.1967	21.56	32.84
- 1b	51	21.3389	16.15	26.53
- 1c	22	9.20502	5.54	12.87
- 2	32	13.3891	9.072	17.71
- 3	69	28.8703	23.13	34.62

Meanwhile, the NLR had a mean of 8.5, with an SD \pm 6.8 (minimum of 1; maximum of 31). The CRP had a mean of 47.46 mg/dL, with an SD \pm 60.7 mg/dL (minimum of 0.50 mg/dL; maximum of 316 mg/dL).

A ROC curve was performed to determine the most precise cut-off point for each of the variables. The following values were found: Leukocyte count > 11,000/m³; neutrophil percentage > 85%; CRP > 15mg/dL; percentage of lymphocytes > 10%; and NLR > 5.5 (**Figure 2**).

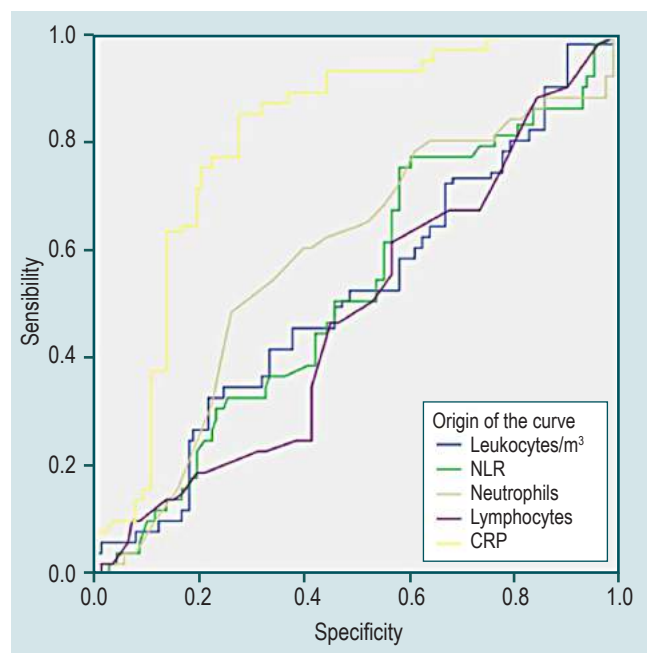


Figure 2. ROC curve

Diagnostic tests

In total, 101 people had severe grades of appendicitis, equivalent to 42.2% of people having appendiceal perforation. According to the results, patients with a percentage of neutrophils > 85% are two times more likely to have intestinal perforation, while patients with CRP > 15 mg/dL are 14 times more likely to have this complication (**Table 2**).

Table 2. Tetrachoric table between the paraclinical with histopathology

Paraclinical test	Acute appendicitis		Diagnostic OR	95% CI
	Perforated (n = 101)	Not perforated (n = 138)		
Leukocyte count > 11,000	79 22	107 31	1.04	0.56;1.93
Neutrophil percentage > 85%	55 46	47 91	2.17	1.28;3.66
Lymphocyte percentage > 10%	68 33	93 45	0.99	0.57;1.72
NLR > 5.5	62 39	78 60	1.22	0.82-1.52
CRP > 15 mg/dL	88 13	44 94	14.46	7.3;28.6

Characteristics of diagnostic tests

Lastly, we found that the tests with the greatest capacity to detect people with appendiceal perforation (sensitivity) were CRP and leukocyte count greater than 11,000/mm³, with 87.13% and 78.22% data, respectively (**Table 3**).

We could determine that the tests with the best capabilities to detect people with non-perforated appendix

(specificity) were CRP and the percentage of neutrophils > 85%, with 68.12% and 65.94% data, respectively (**Table 3**). Finally, the highest diagnostic accuracy test was CRP, with 76.15% (**Table 3**).

DISCUSSION

In the present study, the population studied represents a relatively young population, with an average of 26.35 years. It allows comparing it with other epidemiological data from other studies, as is the case of Cánovas *et al* and Escalona *et al*, who determined that the average age of appendicitis was 21 and 29 years, respectively^(24,25). Therefore, no significant difference in the results obtained marks a great difference from Jonge *et al*'s study, with an average of 55 years⁽²⁶⁾.

Moreover, most people diagnosed with AA were women, 53% of the population, consistent with the results shown by other publications, such as Jonge *et al*'s⁽²⁶⁾, in which the base population was female (51.2%). Even so, in other studies, most patients are male, as is the case of Padierna *et al*'s, with 50.81%⁽²⁷⁾. However, there are no significant differences in gender regarding AA. It should be mentioned that the female sex presents a greater difficulty for diagnosis during the fertile age or pregnancy^(28,29). Another important characteristic is that more patients come from urban areas than rural areas.

Numerous studies document that the pathophysiological stages of appendicitis can be divided into three groups according to the time of clinical evolution, as follows: Incipient (0-12 hours), acute (12-24 hours), and perforated (24-48 hours)^(1,4,10).

This study did not seek a relationship between clinical evolution and perforation; nonetheless, we compared the results of the different stages of the Guzmán-Valdivia classification⁽³⁰⁾. This comparison indicates that the higher the grade, the greater the severity, just like Martínez *et al*'s

Table 3. Characteristics of diagnostic tests

Operating characteristics	Leukocytes	Neutrophils	Lymphocytes	NLR	CRP
Sensitivity	78.22 %	54.46 %	67.33 %	61.39 %	87.13 %
Specificity	22.46 %	65.94 %	32.61 %	43.48 %	68.12 %
Positive predictive value	42.47 %	53.92 %	42.24 %	44.29 %	66.67 %
Negative predictive value	58.49 %	66.42 %	57.69 %	60.61 %	87.85 %
Diagnostic accuracy	46.03 %	61.09 %	47.28 %	51.05 %	76.15 %
Likelihood ratio of a positive test	1009	1599	0.999	1086	2733
Likelihood ratio of a negative test	0.9697	0.6907	1002	0.8881	0.189

research, which obtained the following results: Grade 0: 4; Grade 1A: 26; Grade 1B: 32; Grade 1C: 27; Grade 2: 22; and Grade 3: 11, for a total of 122 patients⁽³¹⁾.

From these results, we could determine that they were superior in our study at a percentage level, with a percentage difference in Grades 1A (5.88%) and 3 (19.96%). They suggest that the most severe complication, perforation with generalized peritonitis, occurred more frequently compared to the study above. Other studies found that perforation had a prevalence of 10% (Rigual *et al*)⁽¹⁹⁾ and 24% (Beltrán *et al*)⁽⁴⁾, but it is still higher in this research, with a prevalence of 42.25% in perforations.

Regarding the inflammatory reactants, we found that leukocytosis and neutrophilia were related to the diagnosis of AA. According to the results obtained in this study, a percentage of neutrophils > 85% increases the possibility of an outcome of appendiceal perforation (OR 2.17; 95% CI 1.28-3.66) (**Table 2**). Similarly, an NLR greater than 5.5 over the reference value was found in patients diagnosed with AA (OR 1.22; 95% CI 0.82; 1.52).

It is noteworthy that patients with AA were found to have a significant positivization of the CRP (mean of 47.46 mg/dL). For this study, the population with a CRP > 15 mg/dL had statistically significant OR (OR 14.46; 95% CI 7.3-28.6), which corroborates the findings in other publications. About the usefulness of this marker as a diagnostic aid, the research by Ishizuka *et al* analyzed the relationship of NLR with gangrenous and perforated appendicitis in 314 patients. It established a figure of eight as the cut-off point, with a sensitivity and specificity of 73% and 39%, respectively⁽³²⁾, results lower than our study's.

Therefore, we can conclude, according to the results of this study, that the diagnostic tests with better operating performance in the emergency department for a patient in whom AA is suspected are CRP (sensitivity: 87.13%; specificity: 68.12%; diagnostic accuracy 76.15%) and the percentage of neutrophils > 85% (sensitivity: 54.46%, specificity: 65.94%, diagnostic accuracy: 61.09%). These results are similar to previous studies, such as Aguirre *et al*'s, where there is a similarity regarding the relationship of CRP and eosinophilia with the pathology, as described in this article⁽²⁸⁾. Overall, the results provide us with valuable tools in daily clinical practice; however, we believe that there is a greater need for research in this field to achieve uniformity in information nationwide and obtain tools that enable us to address issues such as AA even earlier.

In the study by Padierna *et al*, only the CRP and the leukocyte count were compared as predictors of severity. Their results for the CRP showed a sensitivity of 98.3% and a specificity of 88.9%, and for the leukocyte count, a sensitivity of 80% and specificity of 61%⁽²⁷⁾. The CRP results obtained are consistent with such research, but there is a significant

difference in the leukocyte count since the sensitivity of 78.22% and specificity of 22.46 % were obtained, with a diagnostic accuracy of 46.03%. Thus, the results are uneven in this study, and this leukocyte count should not be one of the mainstays to determine the prognosis in the emergency department due to its low specificity.

The study by Acharya *et al* evaluated CRP (sensitivity of 75%; specificity of 50%), the leukocyte count (sensitivity of 79%; specificity of 55%), and other paraclinical tests, such as bilirubin, procalcitonin, IL-6, and urinary serotonin, as other diagnostic and prognostic factors of AA⁽²⁹⁾. In this case, the leukocyte count had a higher value than the CRP, a notable difference based on the results obtained and the rest of the literature reviewed. These results could be explained by the multiple limitations of the study and the potential sources of bias due to the blinding of researchers in the literature.

It is important to highlight that according to the study by Prasetya *et al*, the NLR had high diagnostic accuracy for AA in children, with percentages of sensitivity of 84.6% and specificity of 56.5%, these being higher than those obtained in our study (61.39% and 43.48%, respectively). This finding is probably due to the difference in the age of the study population (18 years as a maximum) and because this is a retrospective study. This limitation should be considered when interpreting results⁽³³⁾.

CONCLUSIONS

Currently, AA is a challenge for diagnosis and prognosis in the emergency department, both for the general practitioner and the specialist, because there is still no marker to define how advanced the pathology is and its potential complications. However, this study could determine the operating characteristics of the inflammatory reactants as predictors of severity in AA and thus prevent possible complications. It was found that CRP has the highest specificity and sensitivity and is also the most positive OR predictor compared to the rest of the reactants.

It also revealed that a leukocyte count greater than 11,000/mm³ and a percentage of neutrophils > 85% were related to the diagnosis of AA. According to the results obtained in this study, a percentage of neutrophils > 85% increases the possibility of a complication (OR 2.17), while a CRP greater than 15 mg/dL increases the possibility of a complication (OR 14.46). This characteristic could be definitive to find the probabilities of AA complications in any age group.

In short, this study could determine the cut-off points of paraclinical variables widely used to predict and prevent AA complications, such as perforation, optimizing in-hospital management and ultimately impacting final care costs and recovery times for patients.

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Usefulness of the Liver Fibrosis Index (LFI) Measured during Endoscopic Ultrasonography in Evaluating the Pancreatic Parenchyma

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Abstract

Endoscopic ultrasound has changed the evaluation of pancreatic diseases and has achieved a histopathological diagnosis (when associated with a puncture); however, this procedure requires training, is not free of complications, and around 25 % of patients may have false negatives. Therefore, quantitative elastography with the strain ratio has been implemented to differentiate benign masses from malignant ones. There is growing but not yet conclusive evidence, given the heterogeneity of the results (without consensus on its performance). It is necessary to develop other methods that allow for greater diagnostic certainty, such as the liver fibrosis index (LFI) measured by endoscopic ultrasonography. This method is based on artificial intelligence and validated for diagnosing and monitoring liver fibrosis. Our group considers that it could also be used to assess the pancreatic parenchyma. **Aim:** To evaluate whether the LFI can differentiate three types of pancreatic tissues: normal pancreas, fatty pancreas, and pancreatic cancer. **Materials and methods:** Prospective cross-sectional single-center study. We included sixty-six patients over 18 years of age with an indication for endoscopic ultrasonography. Group 1 consisted of patients with an indication other than the biliopancreatic disease (55 patients). The endoscopic ultrasonography (EUS) fatty pancreas classification scale was applied to this group, taking the echogenicity of the spleen (previously validated) as a reference; this group was subdivided into normal pancreatic parenchyma and fatty pancreas. Group 2 (11 patients) included those examined for solid pancreatic lesions with a positive cytological diagnosis of pancreatic carcinoma. We used a Google Form as a data collection tool, available with a shortened address (shorturl.at/pIMWX). It was filled out before and after the procedure by Gastroenterology fellows, previously trained for this purpose. The LFI was measured in the pancreas in real-time using software supplied by the manufacturer (Hitachi Noblus) between January 2019 and January 2020. All patients underwent a complete biliopancreatic echoendoscopy, with a linear Pentax echoendoscope and Hitachi Noblus processor. Then, qualitative and quantitative elastography was performed, including LFI measurement. **Results:** We included a total of 66 patients: 11 with a diagnosis of pancreatic cancer confirmed by cytology and 55 sent for ultrasound endoscopy due to pathologies other than the biliopancreatic disease. The age range was 23-89, with a mean of 56.75 years. The most frequent history was steatosis or steatohepatitis ($n = 14$) (25.45 %). The most frequent indication for performing the procedure was subepithelial lesion ($n = 29$) (52.73 %). The percentages of patients according to pancreatic echogenicity were Grade I ($n = 29$) (52.73 %); Grade II ($n = 5$) (9.09 %); Grade III ($n = 18$) (32.73 %); Grade IV ($n = 3$) (5.45 %). Grades I and II were taken as a normal pancreas and Grades III and IV as a fatty pancreas, divided into $n = 34$ patients (61.82 %) for a normal pancreas and $n = 21$ (38 %) for a fatty pancreas. According to the scale used, there is a fatty pancreas prevalence of 38.18 %. The LFI was measured in three subgroups: those considered endoscopically normal, those classified as fatty pancreas, and patients diagnosed with pancreatic cancer confirmed by cytology taken from the pancreas. The LFI for these groups were, respectively, normal pancreas: LFI 2.60, range 0.97-3.47 (95 % CI 2.17-3.02); fatty pancreas: LFI 3.87, range 2.5-5.5 (95 % CI 3.44-4.29); pancreatic cancer: LFI 6.35, range 5.8-7.8 (95 % CI 5.92-6.77). **Conclusions:** This is the first pilot study that applies the LFI to the pancreatic parenchyma. It is useful in differentiating a normal pancreas, a fatty pancreas, and pancreatic carcinoma non-invasively. This finding must be validated in larger and more heterogeneous populations.

Keywords

Endoscopic ultrasonography, elastography, liver fibrosis index, fatty pancreas, pancreatic steatosis, pancreatic cancer.

INTRODUCTION

Despite the exponential growth of medical knowledge and technological and scientific progress in diagnostic methods and treatments, pancreatic diseases remain poorly understood, posing a diagnostic challenge. Symptoms are usually nonspecific or nonexistent (until advanced stages) because the retroperitoneal location of the pancreas makes its exploration difficult using traditional diagnostic imaging techniques. Considering that pathologies such as chronic pancreatitis, pancreatic cancer, and, more recently, fatty pancreas have been increasing in incidence and morbidity and mortality^(1,2), new diagnostic methods are required to diagnose them earlier and more accurately and provide timely treatment.

In 1980, DiMagna *et al* and Hisanaga *et al* developed endoscopic ultrasonography (EUS)^(3,4). Since then, it has become a diagnostic and therapeutic tool in pancreatic diseases, which better assesses the entire parenchyma, with reported sensitivities of 87–100%^(5,6). It has achieved better performance when compared to computerized axial tomography and magnetic resonance imaging⁽⁶⁻⁸⁾. Moreover, EUS plus fine-needle aspiration (EUS-FNA) has become the method to diagnose solid lesions in the pancreas, including pancreatic cancer, especially in lesions smaller than 30 mm, reaching a sensitivity of 93%^(6,9,10). However, up to 25% of patients may have false negatives, depending on various factors (type of needle, technique, experience, availability of a pathologist in the room, among others), added to its complications (such as pancreatitis and bleeding) and high cost (needles between USD 500 and 800), forcing the exploration of new cost-effective, non-invasive diagnostic methods with more outstanding performance. Therefore, EUS plus elastography has been explored as a complementary method.

Elastography evaluates tissue elasticity by ultrasonography, magnetic resonance, or optical coherence tomography⁽¹¹⁾. It has shown its usefulness in the breasts⁽¹²⁾, prostate⁽¹³⁾, and thyroid^(14,15), as well as to guide or avoid biopsies of tissues, especially the liver. Although biopsy has been considered the gold standard for determining the fibrosis index, its use is limited by the invasiveness of the method (with significant morbidity and mortality), costs, and error in taking the sample, making it challenging to monitor the progression of fibrosis⁽¹⁶⁾.

Currently, transient elastography (FibroScan™) has made it possible to establish the degree of fibrosis non-invasively, making it a widely used method^(16,17). It is less sensitive in patients with ascites, abundant adipose tissue, narrow intercostal spaces, and liver atrophy^(18,19) with a significant intra- and interobserver variability depending on the compression of the probe and less accuracy in the diagnosis of moderate fibrosis^(17,19,20). Therefore, real-time

elastography (RTE) has emerged as the evolution of transient elastography, which may be more sensitive in diagnosing the degree of liver fibrosis. It will accurately determine that a liver fibrosis index (LFI) greater than 2.56 correlates with METAVIR scores of F4^(21,22), even in the presence of inflammation⁽²³⁻²⁷⁾.

In the pancreas, RTE-EUS better characterizes different pathologies, such as chronic pancreatitis, fatty pancreas, and pancreatic cancer, by evaluating the rigidity of the pancreatic tissue with a color scale (qualitative elastography)^(28,29). In this field, pancreatic steatosis, an entity described in cadavers in 1926 and documented 40 years later concerning age and obesity^(30,31), has been classified as congenital and acquired. The latter is associated with obesity and metabolic syndrome, called pancreatic steatosis or nonalcoholic fatty pancreas disease^(32,33). The consequences are still under study; however, a relationship has been found with pancreatic cancer development, increasing its relevance^(34,35).

Our group considers it could be used the same way but to assess the pancreatic parenchyma. In this pilot study, our objective is to assess whether the LFI measured by RTE-EUS is useful for differentiating normal, fatty, or cancerous pancreatic tissue in a cohort of patients evaluated using EUS.

MATERIALS AND METHODS

Study design and population

A prospective cross-sectional study was carried out at the University Hospital, a reference center for Gastroenterology and Ultrasound Endoscopy in Bogotá, Colombia, between January 2019 and January 2020. A total of 682 endoscopic ultrasounds were performed in patients who met the following criteria.

Inclusion criteria

- Age equal to or older than 18 years (for both groups)
- Patients referred for diagnostic ultrasound endoscopy without a history of the biliopancreatic disease (subepithelial or mucosal lesions, among others) (Group 1)
- Patients sent for biopsy of solid pancreatic lesions, suspicious of cancer, whose cytology confirmed adenocarcinoma of the pancreas (Group 2)
- Signed informed consent

Exclusion criteria

- Patients with a history of acute or chronic pancreatitis
- Patients who underwent an endoscopic ultrasound biopsy, but the pathology did not confirm the tumor

- Patients with biliopancreatic disease other than cancer
- Patients with portal hypertension of any etiology
- Patients without a spleen
- Patients with biliopancreatic anatomical alteration
- Patients with decreased functionality greater than four on the Eastern Cooperative Oncology Group (ECOG)⁽³⁶⁾ scale
- Patients at risk of bleeding, with an international normalized ratio (INR) > 1.5 or with a platelet count < 50,000/mm²
- Pregnant woman
- Patients under 18 years of age
- Patients who did not authorize the inclusion of their data in the study

Following the criteria, 66 patients were included for analysis (**Figure 1**).

Intervention

Patients who received endoscopic ultrasonography indicated by their treating physician, both inpatient and outpa-

tient, and did not meet any of the exclusion criteria were questioned before the procedure, following a virtual form-type data collection tool. It gathered the demographic data, indication for the study, and the patient's relevant history. A specialist in Internal Medicine and Gastroenterology fellow, previously trained to fill out the virtual form, simultaneously recorded the data obtained during the study. These data were downloaded, corrected, and entered into SPSS software (version 12.0; SPSS Inc).

In all patients, endoscopic ultrasonography was performed following the quality indicators of the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology⁽³⁷⁾. They were carried out in the Gastroenterology ward of a reference unit for diagnostic endoscopic procedures under sedation guided by an anesthesiologist, with a combination of propofol and remifentanyl, titrated according to each patient's characteristics, after examination by the Anesthesiology service.

All procedures were performed with a Pentax linear echoendoscope (EG3870UTK; Pentax, Tokyo, Japan), combined with a portable Noblus color Doppler ultrasound system (Hitachi Aloka Medical, Tokyo, Japan), including

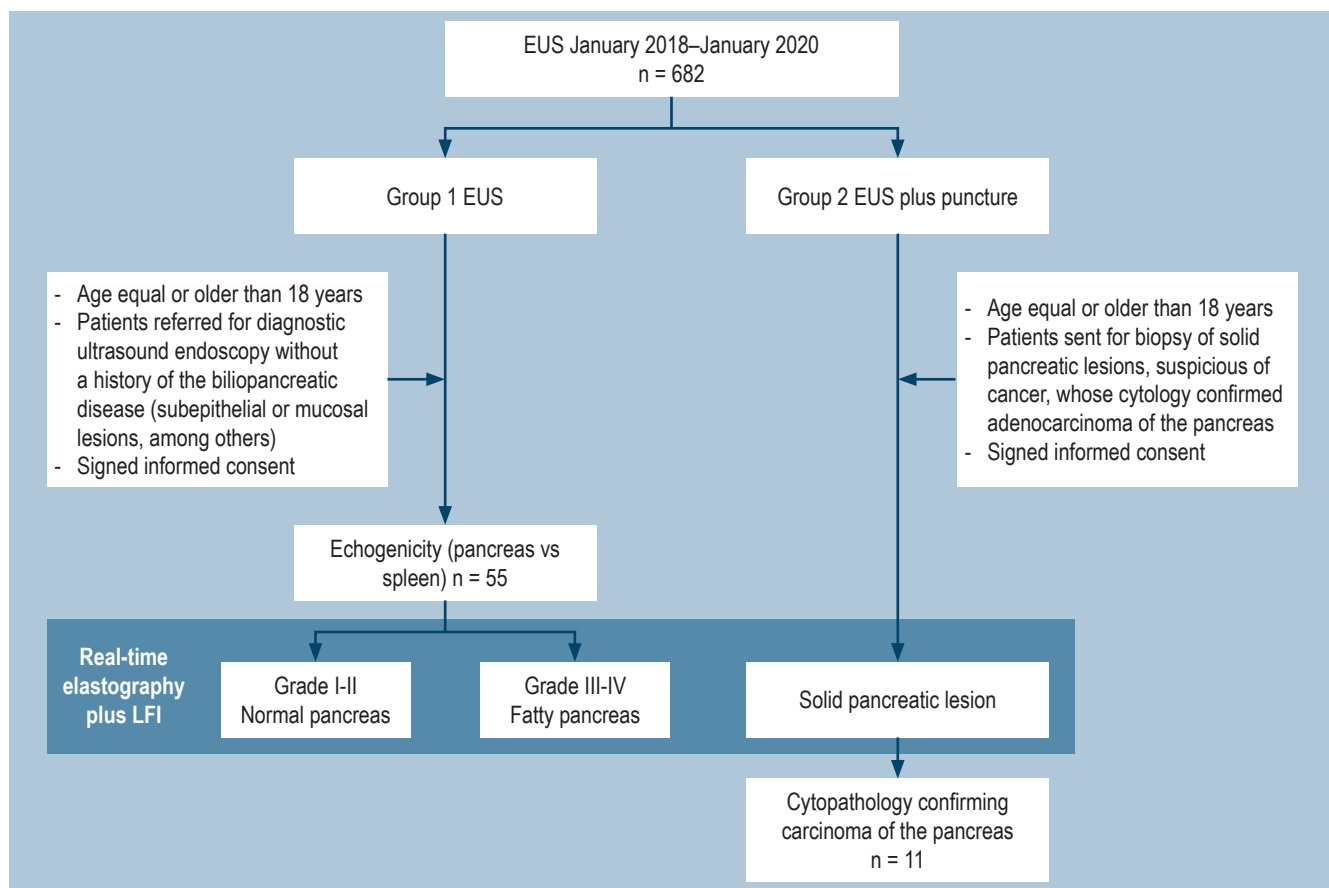


Figure 1. Diagram of the study's basic design.

the elastography module and another LFI module supplied by the manufacturer. An endoscopist experienced in interventional procedures, with more than 2,000 diagnostic and therapeutic EUSs, performed all EUSs.

The pancreatic parenchyma was evaluated during the examination, while the echogenicity was classified into Grades I to IV. The classification system was adapted from Sepe *et al*⁽³⁵⁾. Besides echogenicity, the salt-and-pepper pattern of the pancreatic parenchyma and the clarity in delimiting the pancreatic duct were assessed. Grade I was defined as a pancreas in which more than 80% of the parenchyma is hypoechoic or isoechoic compared to the spleen, the major pancreatic duct is visibly outlined, and the salt-and-pepper pattern is observed. Grade II was defined as a pancreas in which more than 80% is hyperechoic compared to the spleen, the major pancreatic duct is visibly outlined, and the salt-and-pepper pattern is observed. Grade III was defined as a pancreas in which more than 80% is moderately hyperechoic when compared to the spleen, the major pancreatic duct is moderately obscured, and the salt-and-pepper pattern is moderately blurred. Grade IV was defined as a pancreas in which more than 80% is severely hyperechoic compared to the spleen, the margins of the main pancreatic duct are severely obscured, and the salt-and-pepper pattern is severely blurred. Grades I and II were considered normal, while grades III and IV as the fatty pancreas (**Table 1**)⁽³⁵⁾.

Table 1. Fatty pancreas classification scale. Taken from⁽³⁵⁾

Grade	
I	Pancreas in which more than 80% of the parenchyma is hypoechoic or isoechoic compared to the spleen. The major pancreatic duct is visibly outlined, and the salt-and-pepper pattern is observed.
II	Pancreas in which more than 80% is hyperechoic compared to the spleen. The major pancreatic duct is visibly outlined, and the salt-and-pepper pattern is observed.
III	Pancreas in which more than 80% is moderately hyperechoic compared to the spleen. The major pancreatic duct is moderately obscured, and the salt-and-pepper pattern is moderately blurred.
IV	Pancreas in which more than 80% is severely hyperechoic compared to the spleen. The margins of the major pancreatic duct are severely obscured, and the salt-and-pepper pattern is severely blurred.

LFI taken for the pancreas was estimated three times during endoscopic ultrasonography in all patients to limit selection bias. The mean value of the three measurements was considered the final result of the analysis. As previously described, the LFI considers 11 parameters to find image patterns that assess the stiffness of the liver parenchyma.

It is achieved by simply placing the cursor where we want to measure the LFI. The computer immediately calculates this index by pressing the “Enter” button. It has been used in abdominal ultrasound for the staging of liver fibrosis for approximately a decade using elastography images (RTE).

The sequential LFI is completed as follows:

1. Convert the selected analysis area of the RTE image to a 256-frame color scale image.
2. Plot the voltage histogram.
3. Calculate the mean of the relative stress (mean), the standard deviation of the relative stress (SD), the skewness of the strain histogram (SKEW), and the kurtosis of the strain histogram (KURT).
4. Binarize the RTE image into black and white regions: White as low voltage (blue) and black as all other regions.
5. To characterize the low-stress regions (blue), calculate the proportion of low-stress regions within the selected analysis area (area%) and the complexity of the low-stress region (COMP).
6. Calculate entropy (ENT).
7. Calculate the inverse difference moment (IDM) and angular second moment (ASM) to assess the texture of the RTE image
8. Perform multiple regression analysis to improve diagnostic accuracy using all of these imaging features, rather than diagnosing with individual imaging features, as shown in the following multiple regression equation⁽²³⁾:

$$\text{LFI} = -0.009 \times \text{MEAN} - 0.005 \times \text{SD} + 0.023 \times \text{Area \%} + 0.025 \times \text{COMP} + 0.775 \times \text{SKEW} - 0.281 \times \text{KURT} + 2.083 \times \text{ENT} + 3.042 \times \text{IDM} + 39.979 \times \text{ASM} - 5.542$$

This calculation is done in milliseconds with the software, which does not significantly increase the time of the procedure (**Figures 2-4**).

Study variables and definition of variables

Table 2 shows the study variables and their definitions.

Statistical analysis

The database was registered in a virtual form (available on Google Drive with the shortened address shorturl.at/pIMWX). Then, this information was downloaded into Excel data tables, version 2013. We corrected, tabulated, and analyzed the data in the statistical package SPSS, version 2.1. Quantitative variables with normal distribution are presented as the mean and those with abnormal distribution as the median.

The univariate analysis was performed using a descriptive statistic to determine the absolute and relative frequencies

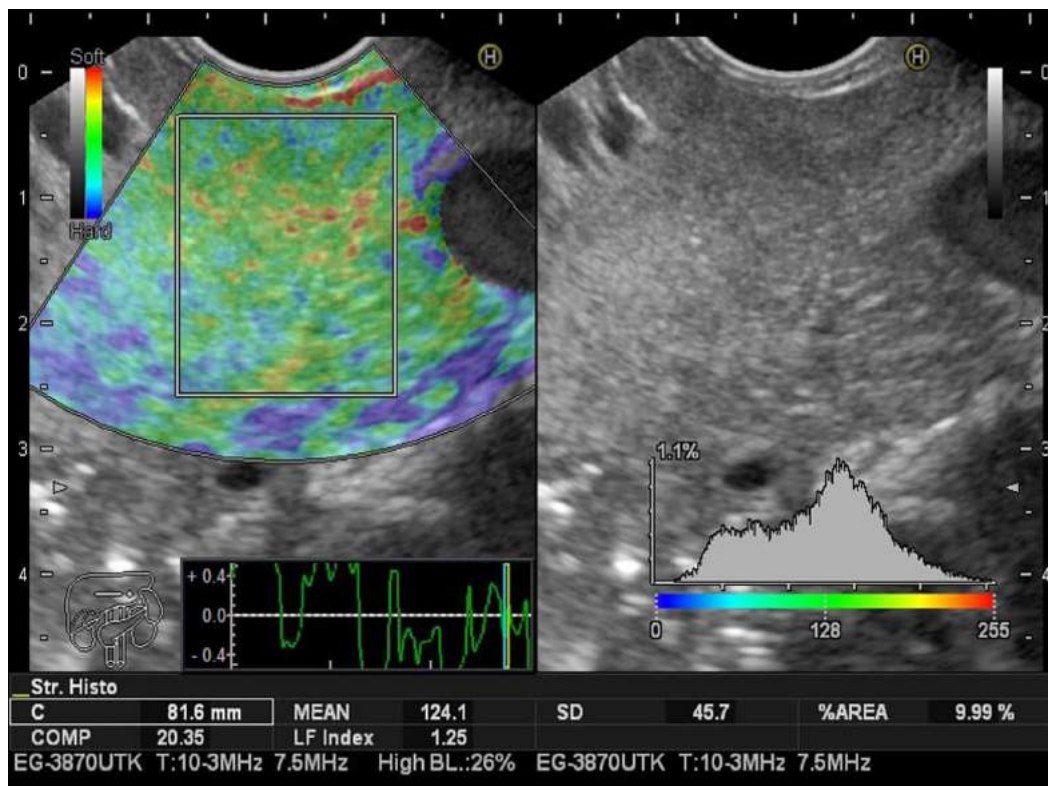


Figure 2. Elastography and LFI in normal pancreas.

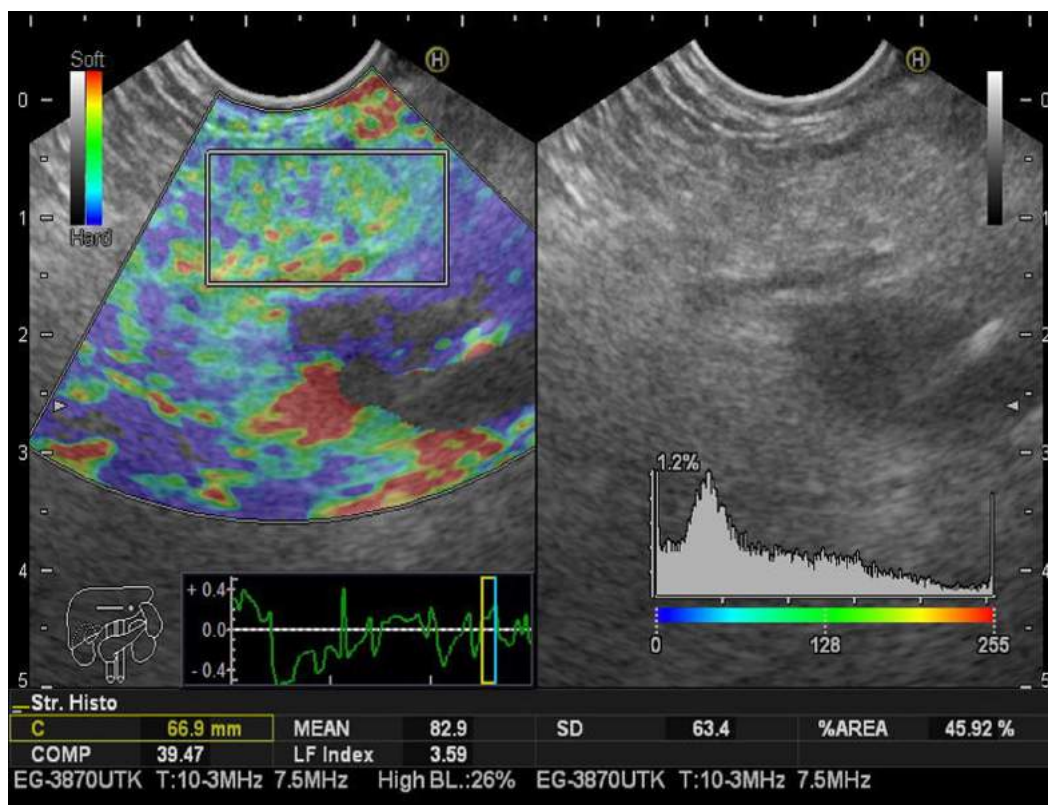


Figure 3. Elastography and LFI in the fatty pancreas.

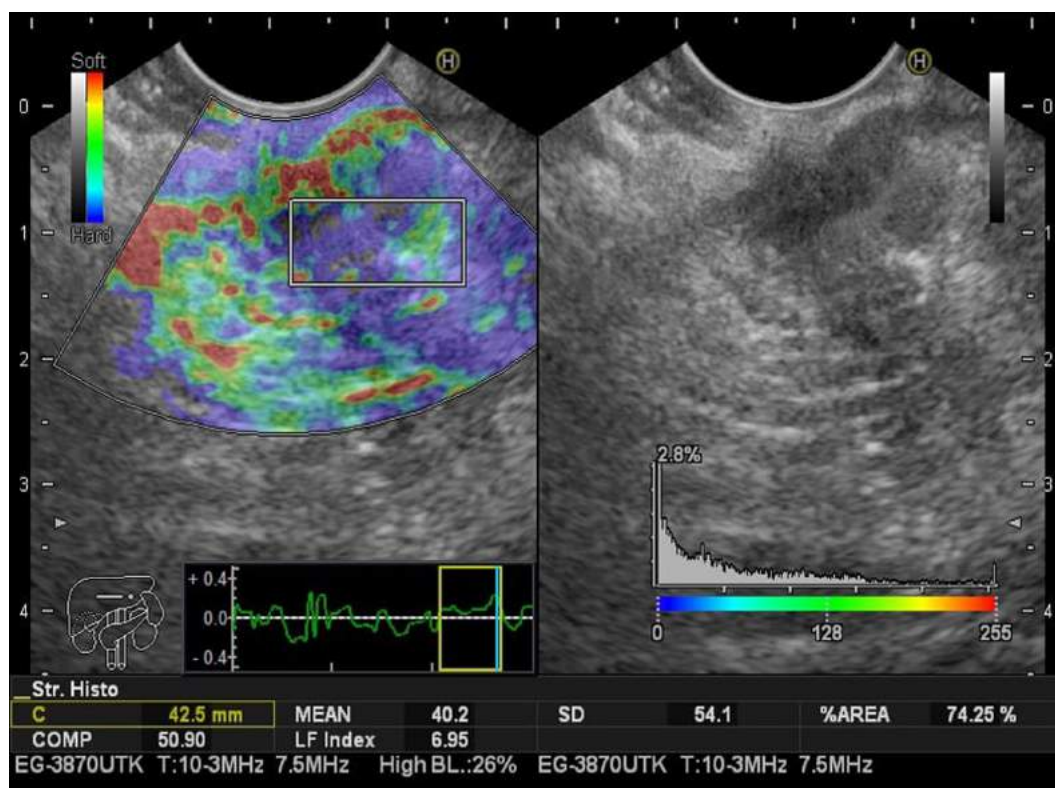


Figure 4. Elastography and LFI in pancreatic cancer.

Table 2. Study variables and definitions

Variable	Nature	Scale	Category
Age	Quantitative	Ratio Discrete	- Years old
Sex	Qualitative	Nominal Dichotomous	- Male - Female
Background	Qualitative	Nominal Polychotomous	- High blood pressure - Diabetes mellitus - Obesity; BMI > 30 - Hypothyroidism - Dyslipidemia - Coronary heart disease - Cerebrovascular disease - Alcohol use (>14 g week) - Hepatic steatosis confirmed by imaging - Other
EUS indication	Qualitative	Nominal Polychotomous	- Indication described by the treating physician
Classification of the fatty pancreas by ultrasound endoscopy	Qualitative	Nominal Polychotomous	- Grade I - Grade II - Grade III - Grade IV
Pancreatic fibrosis index	Quantitative	Continuous	- Fibrosis index value

BMI: Muscle mass index; EUS: Endoscopic ultrasonography.

in the qualitative variables. In the case of quantitative variables, central tendency, dispersion, or position measures were taken (using mean and standard deviation when the numerical variable follows the normal or median distribution).

We calculated the confidence interval for the data set based on the mean, standard deviation, and sample size for the data unit, with a *P*-value equal to 0.05. To determine the normal distribution of the numerical variables, the Kolmogorov-Smirnov statistic (KS statistic) was used, understanding that a *p*-value equal to 0.05 follows the normal distribution curve. An analysis of variance (one-way ANOVA) was performed to determine statistically significant differences between the means of these three groups (normal pancreas, fatty pancreas, pancreatic cancer), which is greater than 0.05. The prevalence will be expressed as a percentage. We sought to determine whether the LFI is different in the normal pancreas, fatty pancreas, and pancreatic carcinoma groups.

Objective

To assess whether LFI can distinguish normal pancreas from the fatty pancreas and pancreatic cancer.

RESULTS

In total, 66 patients were included. Group 1 included 55 patients sent for ultrasound endoscopy to assess pathologies other than a biliopancreatic disease; 32 were women, with an age range of 23-89, the mean age being 56.75 years. Group 2 had 11 patients diagnosed with pancreatic cancer confirmed by cytology, six women and five men, with an age range of 54-89, the mean being 69.56 years. The personal history of this population was high blood pressure, diabetes mellitus, obesity (defined as BMI greater than 30), hypothyroidism, and dyslipidemia, the most frequent being steatosis or steatohepatitis (*n* = 14), the mean being 25.45. The most frequent indication to perform the procedure was subepithelial lesion (*n* = 29). The percentages of patients according to the echogenicity of the pancreas were Grade I (*n* = 29), Grade II (*n* = 5), Grade III (*n* = 18); Grade IV (*n* = 3) (Table 3).

The LFI for the pancreas (mean value of the three measurements), taking Grades I and II as normal and Grades III and IV as fatty pancreas, were, respectively: Normal (*n* = 34), LFI 2.60, range 0.97-3.47; fatty pancreas (*n* = 21), LFI 3.87, range 2-5.5. There is a prevalence for the fatty pancreas of 38.18% when LFI is performed in three different subgroups considered endoscopically normal, fatty pancreas, patients with a previous diagnosis of pancreatic cancer confirmed by histology. The LFI taken in the pancreas was for the three groups, respectively: Normal (Grades I and II): LFI 2.60, range 0.97-3.47 (95% CI 2.17-3.02);

fatty pancreas (Grades III and IV): LFI 3.87, range 2-5.5 (95% CI 3.44-4.29); pancreatic cancer: LFI 6.35, range 5.8-7.8 (95% CI 5.92-6.77) (Table 4).

DISCUSSION

The fatty pancreas is a recently recognized condition that has been little investigated⁽³⁹⁾. Different names have described these changes: Fatty pancreas, fatty infiltration, fatty replacement, and pancreatic lipomatosis. For this article, we have called it a fatty pancreas. Its spectrum ranges from the accumulation of interlobular fat (macrovesicles) to nonalcoholic pancreatic steatosis⁽⁴⁰⁾. Thus, its epidemiology is not yet well defined, given the lack of parameters for a precise diagnosis and, as noted, the apparent differences in terminology to refer to the same entity.

A fatty pancreas is generally deemed an incidental finding during abdominal imaging for other reasons (with no standardized screening test yet). Epidemiological data are limited to the Asian population, and it is estimated that its prevalence may be between 16% and 35%⁽⁴¹⁾. A fatty pancreas has been associated with further development of pancreatic and metabolic complications. An association has been found with type 2 diabetes mellitus, acute pancreatitis (onset and severity), exocrine pancreatic insufficiency, chronic pancreatitis, pancreatic fibrosis, and even pancreatic carcinoma^(35,39-42).

Its pathogenesis is still under investigation, and data are scarce. However, an emerging hypothesis has been proposed that there is a more significant infiltration of macrophages in the pancreatic fatty tissue due to the alteration of the hormonal microenvironment, resulting in a chronic inflammatory condition characterized by the secretion of proinflammatory cytokines (TNF- α and IL-1 β)⁽⁴²⁾. Alternative hypotheses suggest that lipotoxicity resulting from triglyceride accumulation in β cells causes impaired glucose metabolism, leading to cell apoptosis and fat replacement. Paracrine signaling by adipocytes in the pancreas is added, which negatively regulates β cells. All of this alters glucose metabolism, which predisposes to type 2 diabetes mellitus^(41,42).

Pathways affected in acute pancreatitis involve increased production of free radicals, leading to injury and death of acinar cells. They can be replaced by fatty tissue, predisposing patients to develop more severe acute pancreatitis^(32-35,39-42). Finally, concerning pancreatic cancer, a fatty pancreas independently predisposes individuals to develop a pancreatic malignancy. Although the mechanism is unclear, this association may derive from chronic lipogenic inflammation while altering the microenvironment in a protumoral way^(32,34,42).

Assessment of the fatty pancreas includes a histological examination. The fatty infiltration of the pancreas bypasses

Table 3. Demographic characteristics of the study population

	Group 1			Group 2
	Normal pancreas	Fatty pancreas	Total	Pancreatic cancer
Age	n = average (range in years) 57.26 (25-72)	n = average (range in years) 55.90 (23-78)	n = average (range in years) 56.58 (23-78)	n = average (range in years) 69.56 (54-89)
Gender	Normal (n = 34); n = (%)	Fat (n = 21); n = (%)	Total (n = 55); n = (%)	Total (n = 11); n = (%)
- Female	23 (67.65)	9 (42.86)	32 (58.18)	6 (54.55)
- Male	11 (32.35)	12 (57.14)	23 (41.82)	5 (45.45)
History				
- Steatosis or steatohepatitis (confirmed by a previous diagnostic imaging test, ultrasound, MRI, tomography)	6 (17.65)	8 (38.09)	14 (25.45)	
- Hypothyroidism	5 (14.71)	3 (14.29)	8 (14.54)	2 (18.18)
- Diabetes mellitus	4 (11.76)	4 (19.05)	8 (14.54)	5 (45.45)
- Dyslipidemia	4 (11.76)	3 (14.29)	7 (12.73)	
- Alcohol use (more than 14 g per week)	2 (5.88)	2 (9.52)	4 (7.27)	3 (27.27)
- Arrhythmia	1 (2.94)		1 (1.82)	
- Coronary heart disease	1 (2.94)	1 (4.76)	2 (3.64)	1 (9.09)
- Barrett's esophagus	1 (2.94)		1 (1.82)	
- Dyspepsia	1 (2.94)		8 (14.54)	
- High blood pressure	1 (2.94)	2 (9.52)	3 (5.45)	5 (45.45)
- Cerebrovascular disease	1 (2.94)	1 (4.76)	1 (1.82)	
- Kidney failure	1 (2.94)		1 (1.82)	
- No history	6 (17.65)	2 (9.52)	8 (14.54)	
BMI classification. Taken from ⁽³⁸⁾				
- Underweight < 18.5	5 (14.71)	1 (4.76)	6 (10.91)	5 (45.45)
- Normal range (18.5-24.9)	18 (52.94)	5 (23.81)	23 (41.82)	6 (54.55)
- Overweight (25.0-29.9)	8 (23.53)	10 (47.62)	18 (32.73)	
- Obesity (≥ 30)	2 (5.88)	4 (19.05)	6 (10.91)	
- Class I obesity (30.0-34.9)	1 (2.94)	3 (14.29)	4 (7.27)	
- Class II obesity (35.0-39.9)	1 (2.94)		1 (1.82)	
- Class III obesity (> 40)		1 (4.76)	1 (1.82)	
Indication of the procedure				
- Abdominal pain	5 (14.71)	3 (14.29)	8 (14.54)	
- Pancreatic tumor				11 (32.35)
- Gastric neuroendocrine tumor		1 (4.76)	1 (1.82)	
- Gastric extrinsic compression	1 (2.94)		1 (1.82)	
- Subepithelial lesion	20 (58.82)	9 (42.86)	29 (52.73)	
- Unexplained weight loss	2 (5.88)		2 (3.64)	
- Thick gastric folds	3 (8.82)	2 (9.52)	5 (9.09)	
- Gallbladder polyps		1 (4.76)	1 (1.82)	
- Elevated gastric lesion	2 (5.88)	4 (19.05)	6 (10.91)	
- Elevated duodenal lesion	1 (2.94)	1 (4.76)	2 (3.64)	

Table 4. LFI results in the three groups

	Number	Average LFI taken in the pancreas	95% CI (p < 0.05)
Grade I and II	34	2.60	2.17-3.02
Grade III and IV	21	3.87	3.44-4.29
Pancreatic carcinoma	11	6.35	5.92-6.77

95% CI: 95% confidence interval of 2.17-3.02; LFI: Liver fibrosis index.

cer from benign lesions is approximately 75%^(39-43,49), requiring EUS-FNA, which reaches a sensitivity of 89%, specificity of 96%, and diagnostic accuracy of 97%^(37,50-52).

One of the difficulties in EUS-guided puncture is that tissue collection is technically demanding, and multiple punctures may be needed to obtain a sufficient amount of tissue^(47,48). Occasionally, despite repeated sampling, cyto-histological evaluation may be falsely negative and may be associated with small but not insignificant morbidity rates⁽⁵³⁾. Therefore, it is necessary to explore new methods to characterize lesions more precisely but non-invasively, limiting the need for biopsy in the areas with the highest suspicion of malignancy. One of these methods is EUS-guided elastography, which gave rise to the vibration technique in breast ultrasonography^(53,54).

Elastography is based on the knowledge that many pathological processes, such as fibrosis, inflammation, and cancer, induce alterations in tissue stiffness^(12,55,56). This technique assesses stiffness by applying slight compression. Using an ultrasound transducer on the target tissue and recording the displacement of the evaluated region, the physiological and respiratory vascular pulsations provide the vibrations (compressions) necessary for the study⁽⁵⁷⁻⁵⁹⁾.

There are different generations of initially qualitative elastography (colors), which served as the basis for the recently described second-generation elastography by EUS. It enables the quantitative evaluation of tissue stiffness with two different approaches: The strain ratio (SR) and the strain histogram (SH). This RTE-EUS can improve diagnostic performance non-invasively^(44-48,50-56,60-69).

The most studied of these methods is the SR by Itokawa *et al*, being a quantitative elastography technique to differentiate a lesion highly suggestive of cancer, with an average SR of 39.08 or more, from an inflammatory mass, with a mean SR of 23.66 or less ($p < 0.05$)⁽⁶¹⁾. Unfortunately, subsequent studies have not been consistent or reproducible, defining different cut-off values ranging from SR 3.7 to 24, with a sensitivity of 67–98% and with lower levels of specificity of

45–71%. Hence, its application in routine clinical practice is complex^(56,61,62,67). There is a need to assess other methods with more accurate and reproducible results. The answer could lie in the LFI, which, as explained previously, has already been validated, and its usefulness has been demonstrated in the non-invasive diagnosis of liver diseases, with an excellent correlation in measuring the stiffness of the liver parenchyma and detecting fibrosis and fatty liver^(23,25).

As explained above, the LFI is calculated automatically using software that uses the elastography images in real time; 11 variables are included. An initial finding of our work is that a third (38%) of the patients evaluated by EUS have a finding compatible with a fatty pancreas. Nonetheless, as reported in the literature, the prevalence in Asian countries and the United States ranges between 16% and 35%^(55,65). It may be related to the fact that 19% had obesity (BMI greater than 30) and 38% had fatty liver, documented by previous imaging. Of those with a fatty pancreas, more than 30% had some symptom of pancreatic insufficiency. From this study, it is not possible to establish relationships, even though a clear association has been found between nonalcoholic fatty pancreatic disease (NAFPD) with obesity and metabolic syndrome. Fatty degeneration and fibrosis in the pancreatic tissue surrounding most pancreatic adenocarcinomas have also been found^(33,70-72).

Therefore, detecting the fatty pancreas, especially the early detection of pancreatic cancer, is a permanent challenge in clinical practice. It is crucial to have an accurate tool for the early detection of these conditions, allowing timely medical intervention. Our proposal is to use the LFI measured by elastography through EUS.

We carried out this pilot study to evaluate its usefulness in the pancreas. This study found that, as in the liver, there is an association between the increase in LFI and tissue stiffness in the three groups of patients evaluated: Normal pancreas, fatty pancreas, and pancreatic carcinoma. We believe that it could be a useful and more objective tool than the SR if these results can be reproduced in studies with a larger and more heterogeneous population, making it possible to assess its performance in different scenarios of the fatty pancreas in controlled studies.

The main limitation is the sample size, as it is a single-center study with one observer. Being a pilot study with promising findings, it innovates in a field of medical knowledge still in development. It opens the door for new studies that clearly define the usefulness of this diagnostic and follow-up method in this and other settings.

CONCLUSION

This pilot study is the first in the world to use LFI applied to the pancreatic parenchyma. It was shown to help differen-

tiate between normal and fatty pancreas and pancreatic carcinoma non-invasively; however, this finding must be validated in more extensive and heterogeneous populations.

ETHICAL CONSIDERATIONS

This protocol was designed under the current ethical regulations (Declaration of Helsinki, Belmont report, CIOMS guidelines, guidelines for good clinical practice/international harmonization conference GPC/ICH, and, locally, Resolution 8430/1993).

According to Resolution 8430/1993 issued by the Colombia Ministry of Health, it is classified as research with minimal risk. Considering that data collection was based on a review of the videos recorded during the diagnostic procedure or the therapeutic intervention due to the

patient's primary clinical condition, we did not perform any medical intervention, nor did we take contact information from the patient. The patient signed an institutional informed consent form prior to the procedure. The principal investigator of this project collected the information, and all the identity data of the patients were coded. The institutional medical ethics committee approved this document.

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Conflicts of interest

The authors declare no conflict of interest.

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Survival in Patients with Cirrhosis According to Etiology. Retrospective Cohort

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Abstract

Introduction: Cirrhosis is the final stage of chronically progressive liver diseases of various etiologies. It is a common disease, with a variable prevalence in each country. Its peak incidence occurs between 40 and 50 years of age, predominantly in men. **Aims:** To compare a cohort of patients diagnosed with cirrhosis, evaluate their complications and survival according to etiology, describe clinical and laboratory aspects, and determine the role of a fatty liver. **Materials and methods:** A retrospective cohort study was carried out with patients who held a specialized hepatology consultation in the center of liver and digestive diseases (CEHYD) in Bogotá, Colombia, between January 2010 and June 2019. **Results:** We reviewed a total of 1,200 medical records (56.8 % women). There were no statistically significant differences in median survival between groups by etiology, sex, presence or absence of complications, or Child. We noted that the older the age at the diagnosis of cirrhosis, the higher the risk of death; HR 1.04 (95 % CI 1.02-1.075). For each month that follow-up increases, the risk of death decreases by 90 %; HR 0.1 (95 % CI 0.03-0.29). For each month that the follow-up of complications increases, the risk of death is reduced by 2 %; HR 0.98 (95 % CI 0.97-0.99). **Conclusions:** Survival by etiology was similar in the different groups. Nonalcoholic steatohepatitis (NASH) was the leading cause of cirrhosis in this cohort. Efforts should focus on its diagnosis and management in the early stages.

Keywords

Liver cirrhosis, survival, fatty liver, nonalcoholic fatty liver disease.

INTRODUCTION

Cirrhosis is the final phase of progressive and long-term liver disease^(1,2). The prevalence varies in each country, with a maximum incidence between 40 and 50 years, affecting more men⁽²⁾. In Western countries, 90% of cases are due to alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and chronic viral hepatitis, including hepatitis B (HBV) and hepatitis C (HCV). About 10% of the etiology of this entity is unknown⁽¹⁻³⁾.

Cirrhosis is the consequence of the continuous death of hepatocytes, with loss of parenchyma, inflammation, fibrogenesis, changes in cell regeneration, and alterations in macro- and microcirculation⁽⁴⁻⁶⁾. It is a dynamic and reversible process at some point⁽⁷⁻⁹⁾, which has motivated studies in the search for adequate management by identifying and monitoring asymptomatic patients and preventing the entity's complications. Four of them are classic decompensations: Ascites, variceal bleeding, encephalopathy, and jaundice⁽¹⁰⁻¹²⁾.

The manifestation of any of them markedly decreases the survival of cirrhotic patients, being worse with hepatocarcinoma (HCC)⁽¹²⁻¹⁵⁾, which has an approximate annual incidence of 7%^(1,12,15) and is associated with the same causes of cirrhosis, HCV, alcohol, and NAFLD^(1,16-20). Fatty liver is a cause of cirrhosis on the rise^(21,22), directly correlated with elements of the metabolic syndrome. For example, type 2 diabetes *mellitus*, obesity, and high blood pressure, all with increased cardiovascular risk⁽²³⁾. Therefore, this study aims to compare a cohort of patients diagnosed with cirrhosis, evaluate their complications and survival according to their etiology, describe clinical and laboratory aspects, and determine the role of fatty liver.

MATERIALS AND METHODS

We carried out a retrospective cohort study. It included patients who attended a specialized Hepatology consultation at the Center for Liver and Digestive Diseases (CEHYD) in Bogotá between January 2010 and June 2019. Confirmed diagnosis of cirrhosis by the clinic, radiology or liver biopsy, and available medical records were the only inclusion criteria.

Based on the Child-Pugh (CP)⁽²⁴⁾ cirrhosis severity scale, we defined:

- *Compensated cirrhosis*: A Child A stage, without any additional decompensation
- *Decompensated cirrhosis*: A Child B or C stage, or a Child A cirrhosis with ascites, variceal bleeding, encephalopathy, or jaundice

Additionally, ascites, variceal bleeding, encephalopathy, jaundice, HCC, hepatorenal syndrome, or coagulopathy were defined as complications of cirrhosis.

The information collected was summarized using means and standard deviations for a normal distribution (Shapiro-Wilks test); otherwise, it was summarized with medians and interquartile ranges. We performed the analysis with non-parametric statistics and summarized categorical variables as proportions. Survival was assessed based on medians and interquartile ranges. We used the Kaplan Meier estimator of the survival function and the log-rank test. A Cox hazard model was made for the analysis adjusted by the effect of confounding covariates. STATA v15.1 and R were employed for statistical analysis.

ETHICAL CONSIDERATIONS

As a retrospective study, no intentional intervention or modification of the individuals' biological, physiological, psychological, or social variables was carried out. It was conducted under the principles declared at the 18th WMA

General Assembly (Helsinki, 1964) as a world reference for research on human beings. As set forth in Article 11(a), Title II (about research on human beings), Chapter I (about the ethical aspects of research on human beings) of Resolution 008430 dated October 4, 1993, issued by the Ministry of Health of the Republic of Colombia, this study constitutes research without risk. It uses retrospective documentary research techniques and methods, including medical records, interviews, questionnaires, and others, in which sensitive data on illnesses are not identified or processed.

Since it has no risk and only uses documentary research techniques and methods, this study is understood to follow the fundamental principles of ethics: Beneficence, autonomy, justice, and non-maleficence.

RESULTS

We reviewed a total of 1,200 medical records, of which 681 (56.8%) were women. The mean age at diagnosis of cirrhosis was 63 years (interquartile range [IQR] 56–71). The death occurred in 51 patients, with a median age of 75 years (IQR 65–80). The patients were monitored over time, measured in months, with a median of 17.4 (IQR 5.5–45.3). The first complication of cirrhosis occurred in 545 patients (45.4%) 0.7 months after diagnosis (IQR 0–18.1). Complications were, in order of importance, ascites (33.8%), variceal bleeding (22.2%), HCC (17.4%), jaundice (14.3%), encephalopathy (7.3%), ascites plus encephalopathy (2.6%), coagulopathy (2%), and hepatorenal syndrome (0.4%). The clinical and demographic characteristics are shown in **Table 1**.

According to the cirrhosis etiology, the patients were classified into five groups (**Table 2**). The lowest median age at diagnosis of cirrhosis was for the cholestatic group. Furthermore, the alcohol group had a lower median age at death, 64 years. The etiological group with the highest percentage of complications was again alcohol (63.5%), and the lowest was the non-alcoholic steatohepatitis (NASH) group, with 31.6%.

Regarding the severity of cirrhosis at admission, 69.6% had Child A (higher in the NASH group), 21.3% Child B, and 3.9% Child C (higher in the alcohol group).

Table 3 shows, in all patients, a median survival of 34 months (95% CI 29–52). There were no statistically significant differences in median survival between the groups of etiology, sex, presence or absence of complications, or Child. However, higher survival was identified in the cholestatic group (**Figure 1**), being a woman (**Figure 2**), not having a complication (**Figure 3**), and Child C (**Figure 4**), the median survival being 54, 43, 52, and 37 months, respectively.

Considering the variables and the follow-up time illustrated in **Table 4**, the univariate analysis found that as the

Table 1. Clinical and laboratory variables in patients with cirrhosis

Variable	Number	Median (IQR)*
BMI kg/m ²	1139	27 (24 to 30)
White cells (cell/mL)	1154	5500 (4400 to 6890)
Hemoglobin (g/dL)	1153	14 (13 to 16)
Hematocrit %	1153	43 (38 to 47)
Platelets (cell/mm ³)	1155	158 000 (111 650 to 224 500)
Glycemia mg/dL	1087	98 (88 to 115)
AST IU/dL	1158	54 (34 to 90)
ALT IU/dL	1161	50 (31 to 87)
GGT IU/dL	1049	120 (56 to 259)
Alkaline phosphatase IU/dL	1125	132 (95 to 211)
Total bilirubin (mg/dL)	1143	1 (0,6 to 1,7)
Direct bilirubin (mg/dL)	1139	0,4 (0,2 to 0,8)
Indirect bilirubin (mg/dL)	1137	0,5 (0,3 to 0,9)
Total protein (g/dL)	1044	7,3 (6,9 to 7,8)
Albumin (g/dL)	1100	4 (3,4 to 4,3)
INR	1117	1,1 (1 to 1,2)

BMI: Body mass index; INR: International normalized ratio; IQR: Interquartile range tested for normality (Shapiro-Wilk test).

age at diagnosis of cirrhosis increases, the risk of death is higher; *HR* 1.04 (95% *CI* 1.02-1.075; *p* = 0.000633). For each month that the follow-up of cirrhotic patients increases, the risk of death is reduced by 90%; *HR* 0.1 (95% *CI* 0.03-0.29; *p* < 0.00). Similarly, a longer follow-up of complications reduces the risk of death by 2%; *HR* 0.98 (95% *CI* 0.97-0.99; *p* = 0.000695). Finally, the group of other causes of cirrhosis presents a risk of death 3.87 times compared to the cause of cirrhosis due to cholestatic disease (*p* = 0.0386), statistically significant estimates.

DISCUSSION

Studies in the United States showed that in 2010, chronic liver diseases and cirrhosis were the cause of 31,903 deaths, with age-adjusted mortality of 9.4 per 100,000 individuals, and decompensated cirrhosis accounted for more than 150,000 hospitalizations, with a cost close to 4 billion US dollars^(25,26). These data highlight the importance of monitoring the cirrhotic patient.

When reviewing this cohort, the average age of cirrhosis was 63 years, as reported in the Swedish population study by Nilsson *et al*⁽²⁶⁾, with a follow-up of more than 1,000 patients. The highest incidence of the disease occurred in the group of 60–64 years, with a predominance in the female sex, as in our series. In other international series, the male gender predominates, probably due to etiological differences^(27,28).

D'Amico emphasizes a different prognosis in terms of mortality according to the presence or absence of decompensations^(12,28,29). In our cohort, the analysis focused on the presence or absence of complications. Classic ascites, variceal bleeding, jaundice, and encephalopathy⁽¹²⁾ were added to HCC, hepatorenal syndrome, and coagulopathy. In this series, complications occurred in 45.9% of all patients shortly after the diagnosis of cirrhosis (0.7 months) (*IQR* 0-18.1) and with a total follow-up of 17.4 months (*IQR* 5.5-45.3). European series show follow-up periods of up to 10 years or more^(27,28). These two pieces of data alert us to the lateness of our diagnoses since, in most cases, the complication leads to the diagnosis of cirrhosis, and advanced disease does not allow for further follow-up.

In different studies, the survival of patients with compensated cirrhosis is relatively good, with a median of 12 +/- 2 years on average⁽³⁰⁻³²⁾. Our data in patients without complications show a median survival of four years and four months (52 months), well below international data. Although it is higher than the group with complications, it does not present statistically significant differences and could be explained by the number of events analyzed. Moreover, the mortality rate (*HR*) in patients with complications was 1.22 (*CI* 0.58–2.53; *p* not significant), similar to Nilson's study after the first year (*HR* 1.44, *CI* 1.23-1.68)⁽²⁶⁾. Again, these results suggest that our population probably requires more medical follow-up for their cirrhosis.

According to Child (**Table 3**), the results are similar when analyzing survival between 34 and 37 months for the three groups. Although it seemed to be longer for Child C, it favored Child B in the survival curve (**Figure 4**). No statistically significant differences were found in any case. These findings are explained by the low number of events (*n* = 51); however, it is expected that this cohort of patients will be monitored to clarify these results.

Although the survival data by cirrhosis etiology (**Table 3** and **Figure 1**) did not present statistically significant differences, they seemed to favor cholestatic disease (*HR* reference pattern in **Table 4**). Apparently, it is an etiological cause of cirrhosis with a better prognosis, probably due to its onset in childhood or younger populations, with earlier diagnosis, better follow-up, and, in theory, less liver damage⁽³¹⁾. In a study with 9,261 patients, the cholestatic

Table 2. Differences between groups by etiology

Etiology of cirrhosis	NASH n = 399 (33.2%)	Cholestatic n = 245 (20.4%)	Alcohol n = 230 (19.2%)	Other n = 191 (15.9%)	HCV n = 135 (11.2%)	Total n = 1,200 (100%)
Sex*						
- Woman	257 (64.4)	208 (84.9)	27 (11.7)	91 (47.9)	98 (72.6)	681 (56.8)
- Man	142 (35.6)	37 (15.1)	203 (88.3)	100 (52.1)	37 (27.4)	519 (43.2)
Age at first consultation (years) Median (IQR)**	64 (57.8 to 71)	59 (48.7 to 69)	64 (56 to 70)	62 (55 to 70.8)	64 (58.5 to 71)	63 (55 to 70) n = 1200
Age at diagnosis of cirrhosis (years) Median (IQR)**	65 (59 to 72)	60 (48 to 69)	63 (55 to 71)	63 (54.3 to 70.8)	64 (60 to 70)	63 (56 to 71) n = 1200
Age at death (years) Median (IQR)	70 (67.5 to 78.5)	77.5 (72.3 to 80.8)	64 (60 to 78)	74.5 (64.3 to 79.8)	78 (71 to 81.3)	75 (65 to 80) n = 51
Complication*						
- Yes	126 (31.6)	121 (49.4)	146 (63.5)	94 (49.2)	58 (43)	545 (45.4)
- No	273 (68.4)	124 (50.6)	84 (36.5)	97 (50.8)	77 (57)	655 (54.6)
Follow-up of cirrhosis from its diagnosis in months Median (IQR)**	15 (6.3 to 31.3)	28.4 (9.7 to 59.2)	17.3 (3.7 to 47.1)	12.9 (4 to 35)	23 (4.5 to 48.3)	17.4 (5.5 to 45.3) n = 1186
- Follow-up of complications from the diagnosis of cirrhosis in months	0	3.8	0	0.02	5.3	0.7
- Median (IQR)**	(0 to 12)	(0 to 30.6)	(0 to 12)	(0 to 33.13)	(0 to 33.13)	(0 to 18.1) n = 545
Child*						
- A	326 (84.2)	170 (70.8)	125 (58.4)	116 (69.1)	98 (76)	835 (69.6)
- B	50 (12.9)	64 (26.7)	69 (32.2)	47 (28)	26 (20.2)	256 (21.3)
- C	11 (2.9)	6 (2.5)	20 (9.3)	5 (2.9)	5 (3.8)	47 (3.9)
Other: HBV, HCV, and B coinfection, medications, or toxic substances, three or more mixed, HBV plus alcohol						

*Significant differences ($p < 0.005$) between etiological groups of cirrhosis, Fisher's exact test.

**Significant differences ($p < 0.005$) between etiological groups of cirrhosis, Kruskal-Wallis test.

IQR: Interquartile range.

disease had a mortality rate per 100 patients/year of 6.3 (3.1-12.5) below alcohol, virus, and NASH, this being the highest at 15.2 (12.9-17.8)⁽³²⁾. These trends are similar to our study, with HR for alcohol, HCV, and NASH of 1.56, 1.62, and 2.36, respectively (Table 4).

Having other causes of cirrhosis increases the risk of death 3.87 times (Table 4). This group comprises etiological combinations that result in more progressive liver damage. European HCV studies⁽²¹⁻²³⁾ mention that having multiple risk factors, such as viral factors, fatty liver, and

alcohol, increases the likelihood of death, as suggested in other studies^(12,15,27).

Our data show NASH as the primary etiology of cirrhosis (33.2%). The importance of fatty liver as a cause of liver disease and cirrhosis is corroborated by local and international series, where it is shown to displace other etiologies^(11,19,33-37). It must be remembered that worldwide, between 20% and 40% of the population suffers from it. A meta-analysis involving 8,515,431 estimated this global prevalence at 25%, with prevalence rates in South America

Table 3. Survival by group and difference comparison

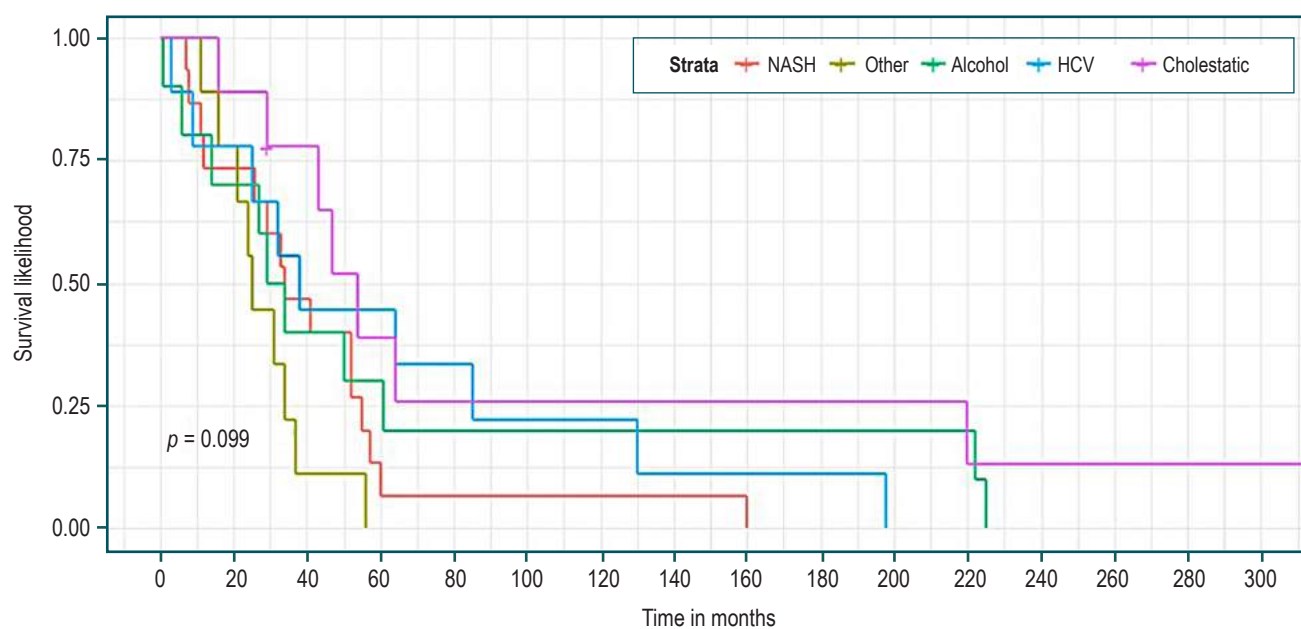
	Number of events	Median survival (95% CI) (months)	Log-rank test
Total	51	34 (29 to 52)	
Etiology of cirrhosis (Figure 1)			
- HCV	9	38 (25 to NC)	$p = 0.099$
- Alcohol	10	31.5 (14 to NC)	
- Cholestatic	8	54 (43 to NC)	
- NASH	15	34 (26 to 57)	
- Other	9	25 (21 to NC)	
Gender (Figure 2)			
- Woman	31	43 (31 to 60)	$p = 0.15$
- Man	20	29 (16 to 50)	
Complications (Figure 3)			
- Yes	42	33 (27 to 50)	$p = 0.58$
- No	9	52 (34 to NC)	
Child* (Figure 4)			
- A	31	34 (25 to 54)	$p = 0.066$
- B	13	34 (29 to NC)	
- C	5	37 (11 to NC)	

NC: Not calculated.

*In two patients, it was not calculated due to a lack of data

Table 4. Differences between cirrhosis groups and follow-up

Follow-up variables	HR (95% CI) (univariate)	
Age at first consultation in years	1.02 (0.99 to 1.04)	$p = 0.096$
Age of diagnosis of cirrhosis in years	1.04 (1.02 to 1.075)	$p = 0.000633$
Follow-up of cirrhosis from its diagnosis in months	0.1 (0.03 to 0.29)	$p < 0.00$
Follow-up of complications after the diagnosis of cirrhosis in months	0.98 (0.97 to 0.99)	$p = 0.000695$
Etiology of cirrhosis		
- Cholestatic	1	
- Alcohol	1.56 (0.59 to 4.12)	$p = 0.3681$
- HCV	1.62 (0.58 to 4.44)	$p = 0.3498$
- NASH	2.36 (0.93 to 5.99)	$p = 0.0695$
- Other	3.87 (1.36 to 11)	$p = 0.0110$
Sex		$p = 0.156$
- Woman	1	
- Man	1.51 (0.85 to 2.68)	
Complications		$p = 0.591$
- No	1	
- Yes	1.22 (0.58 to 2.53)	
Child		
- A	1	
- B	0.48 (0.23 to 1.01)	$p = 0.0556$
- C	1.59 (0.60 to 4.18)	$p = 0.3462$

**Figure 1.** Survival curves by cirrhosis etiology - Kaplan Meier.

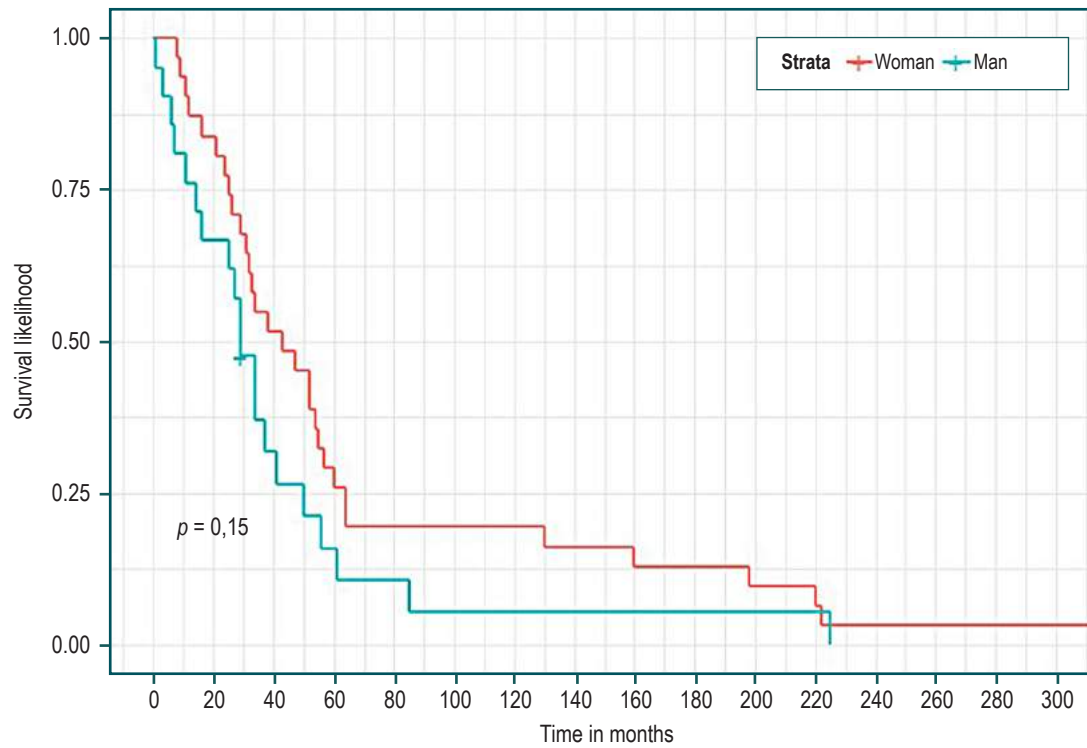


Figure 2. Survival curves by sex - Kaplan-Meier.

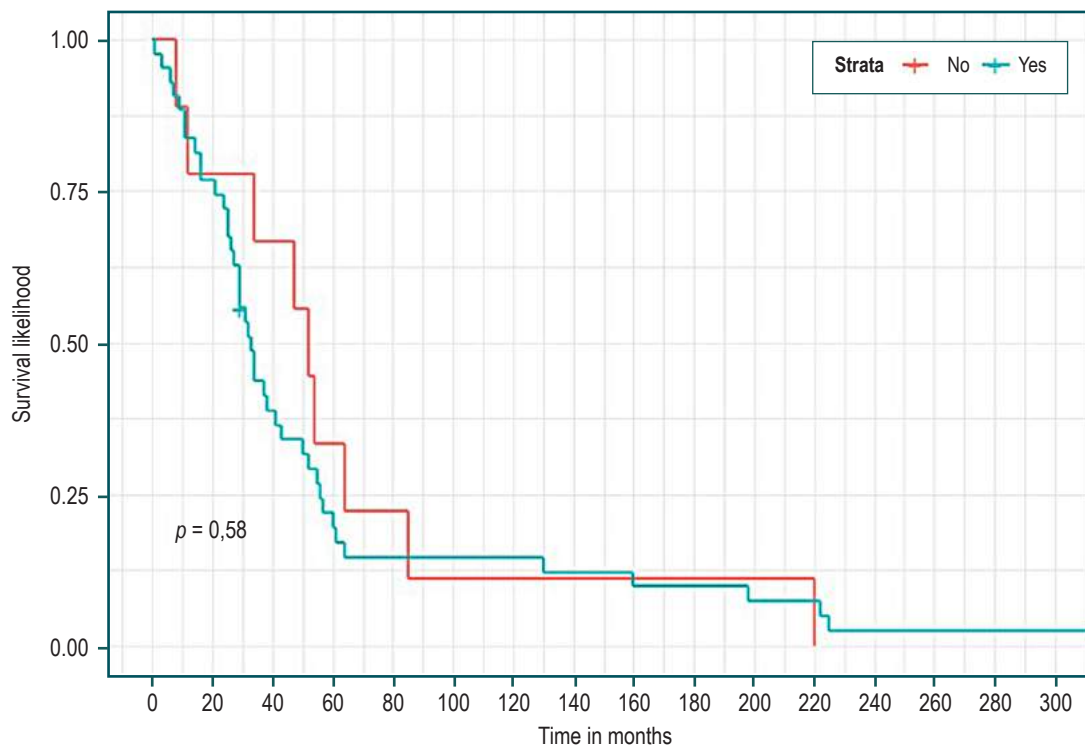


Figure 3. Survival curves by presence or absence of complications - Kaplan Meier.

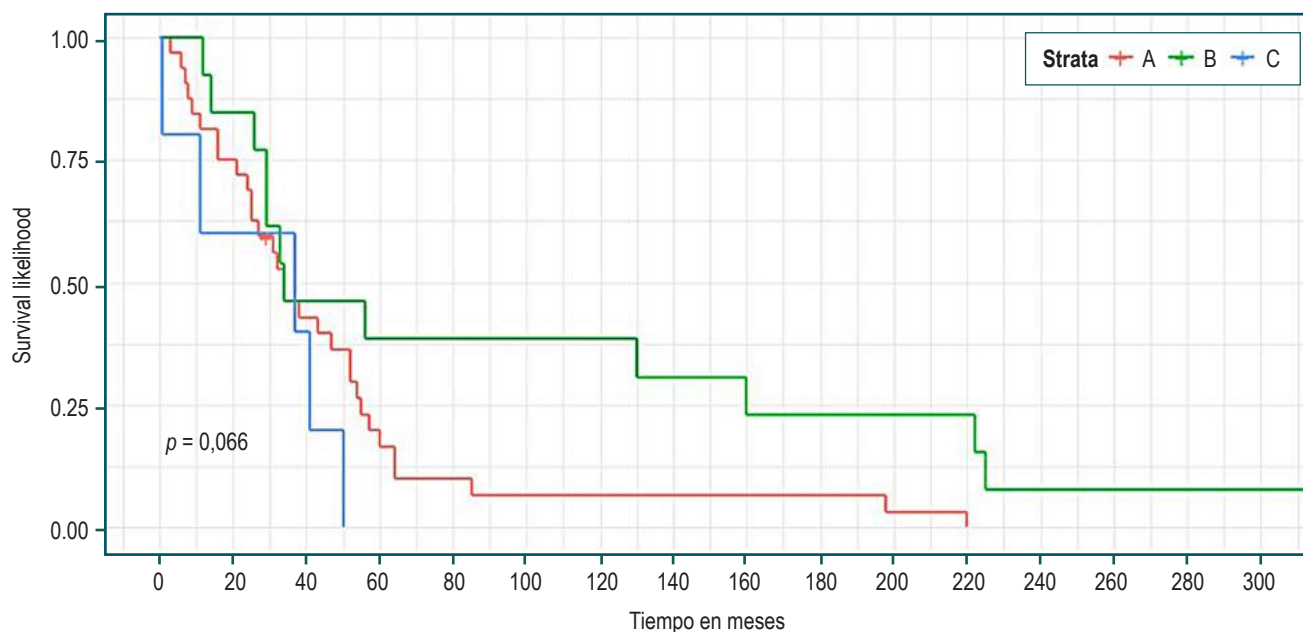


Figure 4. Survival curves by Child - Kaplan Meier.

of 31%⁽³⁸⁾. Therefore, NASH as a cause of cirrhosis and its complications could even be underdiagnosed.

Despite being a single-center study, this is a Colombian cohort of patients under follow-up. It provides research options to learn about our reality and evidence of the fatty liver pandemic and its association with cirrhosis.

CONCLUSIONS

In the present cohort of cirrhotic patients, survival by etiology, gender, or presence/absence of complications did not show statistically significant differences; however, these complications manifest very quickly and alert us to late

diagnoses. NASH was the leading cause of cirrhosis, and efforts should be directed towards its diagnosis and management in the early stages.

Conflict of interests

The authors declare no conflict of interest in conducting this study.

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Experience in the Use of Video Capsule Endoscopy in Patients with Unexplained Iron Deficiency Anemia

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Abstract

Introduction: The prevalence of iron deficiency anemia in developed countries has been estimated between 2-5 %, associated with high morbidity and mortality. Etiological identification is sometimes difficult and requires diagnostic methods, such as video capsule endoscopy (VCE). **Aim:** This study intends to characterize the findings of this technique in patients with unexplained iron deficiency anemia. **Materials and methods:** Descriptive observational retrospective study. We describe the VCE findings (PillCamSB2-SB3) in all patients seen between 2011 and 2019. The findings were interpreted according to the Saurin classification: normal (P0), uncertain potential (P1), and high bleeding potential (P2). **Results:** Of the 490 VCEs performed during the study period, 155 indicated iron deficiency anemia; 106 were women (68.4 %), and the mean age was 57.1 ± 16.6 years. The main comorbidities were cardiovascular in 23 (18.3 %) and arterial hypertension in 16 (12.6 %). Antiplatelets were present in 18 (15.4 %) and anticoagulants in six (5.1 %). Small bowel lesions were vascular in 44 studies (28.4 %), inflammatory in 33 (21.2 %), and neoplastic in seven (4.5 %). Angiectasias were the most frequent lesions in 33 cases (21.3 %). P2 lesions were present in 53 VCEs (34.2 %). **Conclusions:** VCE is helpful in the study of iron deficiency anemia and helps detect positive findings in the midgut in three out of four patients for which it is indicated. The most frequent significant P2 lesions were vascular. These findings allow providing adequate treatment.

Keywords

Capsule endoscopy, small intestine lesions, angiectasias, iron deficiency anemia.

INTRODUCTION

Iron-deficiency anemia occurs in 2% to 5% of adult men and postmenopausal women in developed countries and is the presenting complaint in 4% to 13% of patients in the European community. The leading cause of anemia in premenopausal women is menstrual bleeding, while in postmenopausal women and adult men, it is of gastrointestinal origin⁽¹⁾. According to the World Health Organization (WHO), anemia is a hemoglobin level below 13 g/dL in

men and 12 g/dL in non-pregnant women over 15 years of age. It is regarded as an iron deficiency when ferritin levels are less than 15 µg/L; if an inflammatory disease coexists, a level of less than 50 µg/L⁽²⁾ is considered.

Chronic occult blood loss from the gastrointestinal tract is widely accepted as the main cause of iron deficiency anemia. It can be evaluated by conventional endoscopic methods, such as esophagogastroduodenoscopy and colonoscopy. However, in about 30% of patients with iron-deficiency anemia, its cause is not explained after these studies.

In 5% of patients with overt gastrointestinal bleeding, no lesions are identified with these endoscopic diagnostic studies, thus requiring an examination of small bowel lesions with diagnostic methods, such as video capsule endoscopy (VCE)^(3,4) and single- or double-balloon enteroscopy⁽⁵⁾. These two studies have similar performance and findings (70.5% vs. 69.6%; $p = 0.9$), if a complete enteroscopy is achieved^(6,7). The agreement between VCE and enteroscopy can also vary depending on the type of lesion found, with good agreement for inflammatory lesions $Ik = 0.71$ (95% CI 0.52-0.91) and moderate agreement for angiectasias, $Ik = 0.45$ (95% CI 0.25-0.65) and tumors, $Ik = 0.40$ (95% CI 0.12-0.68)⁽⁸⁾.

VCE is considered the preferred method by patients and clinicians because it is non-invasive. Enteroscopy is more invasive and has more adverse effects, with complications inherent to the procedure or anesthesia^(9,10). The main complication of VCE is retention in the small bowel, defined as the permanence of the device in the gastrointestinal tract for more than 15 days⁽¹¹⁾. This paper aims to characterize lesions in the small bowel related to the diagnosis of unexplained iron-deficiency anemia.

Different series have assessed the diagnostic performance of VCE in obscure gastrointestinal bleeding, with 57% according to Juliao *et al*⁽¹⁰⁾ and 58% in the series by García del Risco *et al*⁽¹²⁾. In the latter, overt obscure bleeding was present in 68% and occult bleeding in 32%⁽¹²⁾, without discriminating the VCE findings in these patients with anemia without overt bleeding, who are the subject of this study. However, one barrier is that despite being a non-invasive method and having a low rate of adverse events, it represents a high cost. So, this resource is not available in many low- and middle-income countries.

MATERIALS AND METHODS

Study design

This descriptive, observational, retrospective study included all patients over 18 years of age with an indication for VCE due to iron-deficiency anemia between January 2011 and December 2019. Outpatient and inpatient procedures were added. Patients with overt gastrointestinal bleeding were excluded. All patients had negative ileocolonoscopy, esophagogastroduodenoscopy, and positive fecal occult blood test. In addition to demographic variables and VCE findings, we collected information from paraclinical tests, including hemoglobin, iron, and ferritin levels, comorbidities, and drug history, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs, or anticoagulants during the study or within 90 days prior.

VCE procedure

Examinations were performed with the VCE Pillcam SB2 and SB3 (Medtronic). The procedure began by administering the capsule after an 8-hour fast⁽¹³⁾, previously prepared with two sachets of polyethylene glycol diluted in two liters of water^(14,15). At four hours, the patient was allowed to have a light meal. After eight hours, or the time required for the VCE to achieve a cecal image, the recorder was turned off, and the images were downloaded using Rapid Reader software. Three gastroenterologists with training and experience in interpreting VCE performed the assessment.

The VCE findings were interpreted according to the degree of clinical relevance for the final diagnosis, according to Saurin's classification proposal: No potential of bleeding (P0) or absence of lesions; low/uncertain risk of bleeding (P1), including red spots, lymphangiectasia, phlebectasias, erosions, xanthomas, nodular lymphoid hyperplasia; and high bleeding potentials (P2), such as angiectasias, tumors, or ulcers⁽¹⁶⁾. VCE retention was established as non-expulsion within 15 days of performing the VCE⁽¹⁷⁾.

Statistical analysis

Demographic variables are presented as percentages and frequencies; quantitative variables are means with standard deviations ($\pm SD$) in normal distribution and continuous variables and median with interquartile range (IQR) for non-normal distribution variables. We grouped the categorical variables into absolute and relative frequencies, measured in percentages for their description. The Chi² test or Fisher's exact test, as necessary, was used to compare the distribution of qualitative variables, such as lesion grades according to capsule type and age range. We considered a p -value < 0.05 statistically significant. Analyses were performed using STATA 15.0 software. (Statistic Software. College Station, TX: Stata Corp LP).

Ethical considerations

The institutional ethics committee approved the project. Informed consent was obtained from all participants to perform the procedures, following the privacy and reliability principles in patient identification.

RESULTS

Between January 2011 and December 2019, 490 VCEs (PillCamSB2 - SB3) were performed at the institution. We analyzed 155 studies, indicating iron-deficiency anemia of unexplained cause in 153 patients. The mean age was

about 60 years. The female sex represented two-thirds of the population under study; 90% of the studies were outpatient. The primary comorbidities of our patients were cardiovascular, high blood pressure, and gastrointestinal, while one in seven subjects had no medical history. Drug history was not documented in all medical records. Still, among those that documented it ($n = 117$), the most common were antiplatelets (acetylsalicylic acid [ASA] or clopidogrel), followed by oral anticoagulants and heparins. The general characteristics of the patients are shown in **Table 1**.

Table 1. General characteristics of the sample ($N = 155$). Comorbidities ($N = 126$) or drug history ($N = 117$) were not reported in all records

Age (years)	
- Mean (SD)	59.6 (16.8)
- Range	21-88
- Median (IQR)	62 (47-73)
Women (%)	106 (68.4 %)
Area	
- Inpatient (%)	17 (10.9 %)
- Outpatient (%)	138 (89.1 %)
Comorbidities ($N = 126$)	
- Cardiovascular	23 (18.3 %)
- High blood pressure	16 (12.6 %)
- Gastrointestinal	14 (11.1 %)
- Diabetes	7 (5.6 %)
- Hematological/oncological	8 (6.3 %)
- Nephrological	6 (4.8 %)
- Rheumatological	3 (2.4 %)
- Chronic liver disease	2 (1.6 %)
- Other	5 (4.0 %)
Drugs ($N = 117$)	
- Neither	82 (70.1 %)
- Antiplatelets	18 (15.4 %)
- Anticoagulants	6 (5.1 %)
- Heparins	4 (3.4 %)
- Anticoagulants and antiplatelets	2 (1.7 %)
- NSAIDs and antiplatelets	2 (1.7 %)

NSAID: Nonsteroidal anti-inflammatory drug; SD: Standard deviation; IQR: Interquartile range.

The VCEs used were the Pillcam SB3 type in 70 (45.2%) studies. The unobstructed view was achieved in 153 (98.7%), with a mean small bowel transit time of 233 minutes (SD of 117 minutes). Positive findings were identified in 114 (73.6%) procedures. The most frequent lesions were of a vascular etiology, followed by inflammatory and neoplastic causes. Stenosis was found during VCE transit in six cases (3.8%), with retention in four patients (2.6%).

Potential bleeding lesions, characterized as P2 lesions according to the Saurin classification, were found in 53 (34.2%) VCEs. According to the type of VCE, there were

statistically significant differences in the positive findings in the Pillcam SB3 VCE (84.2%) compared to the Pillcam SB2. According to the lesion grade of Saurin classification, the P0 was 32 (37.7%) with Pillcam SB2 and only eleven with SB3 (15.7%) (p 0.0024). P1 lesions were found in 26 (30.6%) with Pillcam SB2 and 33 with SB3 (47.1%) (p 0.0346). In the P2 lesions, there were no statistically significant differences (p 0.4823) in the Pillcam SB2; they were found in 27 (31.8%) VCEs, compared to SB3. Lesions were identified in 26 (37.1%) studies, highlighting a poor view in only two (1.3%) of the Pillcam SB2-type VCEs. No lesions were detected in the latter, but it does not interfere with these findings.

In 63 VCEs (40.6%), flat-looking lesions were identified as angiectasias, lymphangiectasias, and macules. Protruding lesions were found in 27 studies (17.3%); nodules were the most frequent, followed by tumors. Excavated lesions were present in 46 (29.7%). The most frequent type was erosions, followed by ulcers. Of the vascular lesions, the most frequent were angiectasias in 33 studies, followed by ulcers and tumors (**Figure 1** and **Table 2**).

In elderly patients, angiectasias were identified in 26.5% and tumors in 7.2%; ulcers were more frequent in those under 60 years old. P2 lesions with bleeding potential occurred in 42.2% of patients over 60 years of age, with a statistically significant difference (**Table 3**). Protruding lesions interpreted as tumors were identified in seven (4.5%) VCEs. Of these studies, four patients underwent institutional enteroscopy and biopsy of the lesions, with histopathological findings in two patients: One with moderately differentiated adenocarcinoma and the other with Hodgkin's lymphoma. One patient had a lesion that corresponded to lymphangiectasia.

The hemoglobin value within three months before or after the VCE was reported in 64 medical records, with an average of 9 g/dL. Eight patients had normal hemoglobin, according to the WHO definition. Just over half of these patients (33) presented with moderate anemia, defined by a hemoglobin range between 7.0 and 9.9 g/dL in 33 (21.3%), while six had severe anemia (less than 7 g/dL). In these patients with moderate to severe anemia, P1 and P2 lesions, according to the Saurin classification, were found in 29 (51.7%) VCEs. Ferritin level was documented in 20 patients, with a mean value of 30.2 ng/mL (7.9-89.0), and the iron level in 21 patients, with a mean of 22 µg/dL (15.7-27.0 µg/dL).

DISCUSSION

Obscure gastrointestinal bleeding is classified as overt bleeding if there is evidence of bleeding (hematemesis, melena, or hematochezia) or occult bleeding, defined by iron-deficiency anemia or persistently positive fecal occult

blood. Many of these patients pose a diagnostic challenge and require other assessment methods, such as VCE, to identify lesions in the small bowel, which are not within the scope of upper endoscopy or colonoscopy. Unexplained iron-deficiency anemia is a frequent reason for referral to gastroenterology to identify the lesion responsible for bleeding because its recurrence has high morbidity, requires a transfusion, and can lead to mortality.

Due to the complete examination of the entire mucosa of the small bowel in the VCE, the diagnostic assessment has been extended to patients with occult gastrointestinal bleeding, which has allowed identifying the cause in many patients with unexplained iron-deficiency anemia⁽¹⁸⁾. The diagnostic yield in various studies has proven superior to other methods in identifying the source of bleeding. In a meta-analysis of 14 prospective studies in 396 patients with occult gastrointestinal bleeding, VCE was found to have a better diagnostic yield than enteroscopy (56% vs. 28%, $p < 0.00001$) and other radiological studies of the small bowel, such as barium x-ray (67% vs. 8%; $p < 0.00001$).

Compared to the other tests, the number needed to diagnose (NND) in VCE was three (95% CI 2-4). The most significant use was noted in vascular lesions, 36% in VCE compared to 20% in enteroscopy⁽¹⁹⁾. In this study, the most frequent lesions identified were of a vascular etiology in 44 (28.4%) VCEs, specifically in patients with unexplained iron-deficiency anemia without overt bleeding.

Some series have evaluated the diagnostic yield of VCE in overt and occult obscure gastrointestinal bleeding. Chronic anemia was identified in 41% of the patients, as in the series of 100 patients reported by Mosquera *et al* in a tertiary referral center⁽²⁰⁾, without determining the diagnostic yield in patients with unexplained iron-deficiency anemia, which is the subject matter of this study.

A recent retrospective study on 118 patients evaluated the impact of VCE on iron-deficiency anemia; it was diagnosed in 49%. Small bowel lesions were more frequent in those over 60 years of age (60%) compared to 34%, attributable to the higher frequency of angiectasias and inflammatory causes in those under 60, as described in this study,

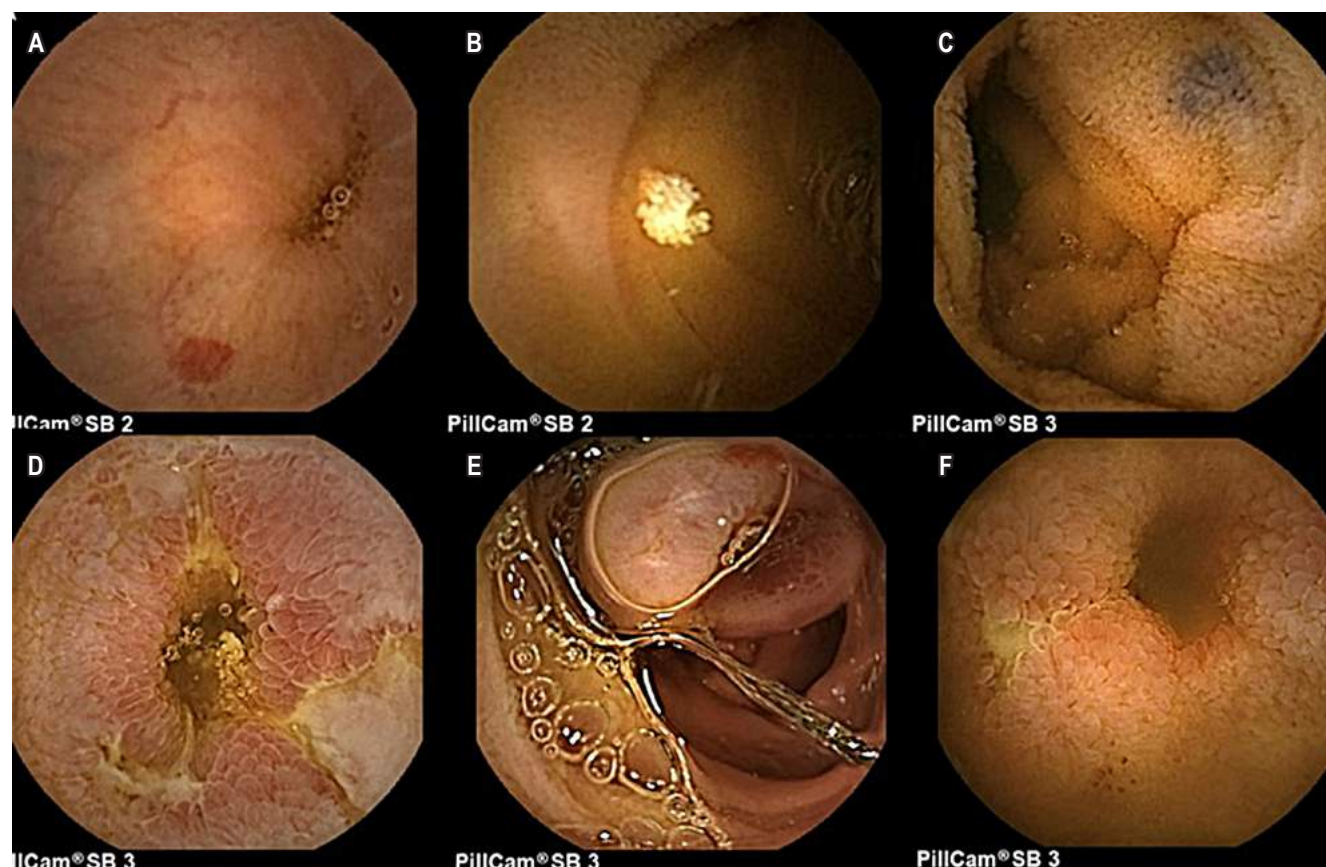


Figure 1. VCE images in patients with unexplained iron-deficiency anemia. **A.** Angiectasias. **B.** Lymphangiectasia. **C.** Phlebectasia. **D.** Fibrin-covered ulcers. **E.** Tumor. **F.** Stenosis. Source: Authors' images.

Table 2. General findings on VCE in patients with unexplained iron-deficiency anemia (N = 155)

Capsule type	
- Pillcam SB2	85 (54.8 %)
- Pillcam SB3	70 (45.2 %)
View	
- Adequate	85 (54.8 %)
- Moderate	68 (43.9 %)
- Inadequate	2 (1.3 %)
Small bowel transit	
- Mean (SD)	233 min (117)
- Rank	42-573 min
- Median (IQR)	210 (144-271)
Small bowel lesions	
- Yes	114 (73.6 %)
- No	41 (26.4 %)
Type of lesion	
- None	41 (26.4 %)
- Vascular	44 (28.4 %)
- Inflammatory	33 (21.3 %)
- Lymphangiectasia	14 (9.1 %)
- Neoplastic	7 (4.5 %)
- Xanthoma	10 (6.4 %)
- Diverticulum	2 (1.3 %)
- Nodular lymphoid hyperplasia	1 (0.7 %)
Lumen	
- Normal	149 (96.2 %)
- Stenosis	6 (3.8 %)
Mucous membrane	
- Erythematous	26 (16.8 %)
- Pallor	21 (13.5 %)
- Nodular	3 (1.9 %)
- Normal	105 (67.8 %)
Flat lesions	
- None	92 (59.4 %)
- Angiectasia	33 (21.3 %)
- Lymphangiectasia	17 (10.9 %)
- Spot	9 (5.8 %)
- Phlebectasia	4 (2.6 %)
Protruding lesions	
- None	128 (82.6 %)
- Nodules	14 (9.0 %)
- Mass/tumor	7 (4.5 %)
- Polyp	6 (3.9 %)
Excavated lesions	
- None	109 (70.3 %)
- Erosion	28 (18.1 %)
- Ulcer	14 (9.0 %)
- Thrush	2 (1.3 %)
- Diverticulum	2 (1.3 %)
Grade of lesion (Saurin classification)	
- P0	43 (27.7 %)
- P1	59 (38.1 %)
- P2	53 (34.2 %)

Table 3. Positive findings on VCE according to age group

	< 60 years N = 72 n (%)	≥ 60 N = 83 n (%)	P-value
Angiectasias	11 (15.3)	22 (26.5)	0.0885
Ulcers	7 (9.7)	6 (7.2)	0.5764
Tumor	1 (1.4)	6 (7.2)	0.1231
Lesion grade			
- 0	21 (29.2)	22 (26.5)	0.7121
- 1	33 (45.8)	26 (31.3)	0.0635
- 2	18 (25.0)	35 (42.2)	0.0246

with evidence of statistically significant P2 lesions in those over 60⁽²¹⁾. Some studies have described a higher frequency of iron-deficiency anemia in patients older than 50 years (OR 1.6; $p = 0.002$; 95% CI 1.2-2.2), more comorbidities, and transfusion requirements⁽²²⁾.

Angiectasias are among the most common causes of iron deficiency anemia in the elderly with comorbidities, such as kidney disease or chronic liver disease, followed by NSAID-induced inflammation⁽²³⁾. The higher performance of VCE has been found in patients older than 75 years compared to a younger population (51.47% vs. 42.76%; $p 0.002$)⁽²⁴⁾. Another study, which assessed the predictive factors of positive VCE findings in patients with iron-deficiency anemia, found an association between male sex (OR 3.93; 95% CI 1.57-9.86), age (OR 1.03; 95% CI 1.0-1.06), and hemoglobin levels less than 9 g/dL (OR 0.73; 95% CI 0.57-0.94)⁽²⁵⁾.

In their study of 109 patients with unexplained iron-deficiency anemia who underwent VCE, Contaldo *et al* documented small bowel lesions in 73.4% of patients, with multiple lesions in 17.5%. The consumption of NSAIDs was associated with lesions (OR 1.13; 95% CI 1.02-1.31; $p 0.049$). The intake of anticoagulants was not statistically significant (OR 3.38; 95% CI 0.73-15.7; $p 0.10$)⁽²⁶⁾.

This study showed positive VCE findings in 73.5% of cases where lesions were documented, with the potential for anemia in 34.2%. More lesions were found with the type of VCE Pillcam SB3 (84.3% of the studies), with statistically significant differences in identifying P1 and P0 lesions with no potential for bleeding. There were no differences between the type of VCE in P2 lesions or with a potential for anemia.

In the literature, VCE has a diagnostic yield of 38-83% in patients with small bowel lesions, with a positive predictive value of 94-97% and a negative predictive value of

83-100% in assessing gastrointestinal bleeding. Its limitations are low specificity and false negatives in 10-36% of cases⁽⁵⁾. The main complication of VCE is retention in the small bowel⁽¹¹⁾. Our study showed stenosis during VCE transit in six patients (3.8%), with retention in four (2.6%). The occurrence was somewhat higher than in other studies, which state that it is less than 2%⁽¹⁷⁾. In a systematic review of 227 studies (a total of 22,840 procedures) by Liao *et al*, the detection rate of small bowel lesions was reported as 59.4% ($p < 0.0001$; 95% CI 56.5-62.2%), lower than in this study. The most frequent lesions were angiectasias in 50%; complications such as retention occurred in 1.4%⁽²⁷⁾.

In a retrospective study conducted by Riccioni *et al*⁽²⁸⁾ to evaluate the usefulness of VCE in 138 patients with unexplained iron-deficiency anemia, VCE identified at least one causal lesion in two out of three patients evaluated. The main findings were angiectasias, followed by jejunal or ileal microulcerations, tumors, erosive gastritis, and Crohn's disease. At the end of the follow-up period, improvement in anemia after intervention and treatment (medical, endoscopic, or surgical) was documented, with complete resolution of iron-deficiency anemia in 96% of patients. In our study, VCE identified positive findings in three out of four studies and showed lesions causing anemia in 34%. Given that these patients were admitted only for the procedure, we could not review their complete medical records, preventing the possibility of assessing the subsequent follow-up of the interventions and treatments performed.

The limitations of our study are retrospective, so it was not possible to tell the patient to stop treatment with NSAIDs prior to the VCE.

CONCLUSIONS

With the results obtained in this work, we can conclude that VCE is a valuable tool in studying patients with unexplained iron-deficiency anemia, in whom upper and lower digestive tract lesions have been ruled out. Positive findings were identified in the midgut that explain the anemia in 34% of cases. The most frequent significant P2 lesions were vascular. These findings allow interventions and appropriate direct treatment.

Data confidentiality

The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare no conflict of interest.

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Can We Use the Indication for a Colonoscopy as a Predictor of the Adenoma Detection Rate?

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Abstract

Aim: To determine the adenoma detection rate (ADR) and identify the indications for a colonoscopy that predict adenomas. **Materials and methods:** Cross-sectional study. We included patients older than 18 years who underwent colonoscopy between February and July 2020 at a specialized center in Medellín, Colombia. We estimated the ADR and identified the indications for a colonoscopy, considered predictors for finding adenomas. **Results:** The overall adenoma detection was 21 % ($n = 992$) and ADR in the screening population was 25 %. The range of 40-49 years contributed 12 % of the total number of adenomas detected, and the male population had a higher incidence ($OR\ 1.73$; 95 % $CI\ 1.25-2.38$; $p < 0.001$). Personal history of polyps ($OR\ 1.86$; 95 % $CI\ 1.25-2.78$; $p = 0.002$) and fecal occult blood ($OR\ 2.67$; 95 % $CI\ 1.12-6.35$; $p = 0.026$) are deemed predictors for finding adenomas. LCI filters showed better results in detecting lesions ($OR\ 1.43$; 95 % $CI\ 1.02-2.0$). **Conclusions:** The indications for a colonoscopy can predict the probability of detecting adenomas. Male gender, a personal history of polyps, fecal occult blood, and the search for adenomas after the age of 40 are the variables that increase the probability of finding adenomas. The use of LCI filters increases lesion detection. The suggested age to start CRC screening is 40 years.

Keywords

Colonoscopy, adenoma, surveillance, screening.

INTRODUCTION

The adenoma detection rate (ADR) is considered one of the leading quality indicators in colonoscopy⁽¹⁻³⁾. It is assessed in asymptomatic individuals or people with an average risk for colorectal cancer (CRC) through colonoscopy⁽⁴⁾. This detection impacts CRC mortality by diagnosing the disease in early and curable stages and is cost-effective^(5,6). Its incidence and mortality have changed because of the starting age of screening through colonoscopy and polypectomy⁽⁷⁾.

Differences in ADR have been reported, depending on whether the indication for colonoscopy is screening, surveillance of CRC precursor lesions, or diagnosis of diges-

tive diseases⁽⁸⁻¹⁰⁾. Significant differences by gender have also been found⁽⁴⁾.

The present study seeks to establish the ADR and identify those indications for a colonoscopy that predict the possibility of adenomas. Characterization of resected colorectal adenomas is not considered within the scope of this study.

MATERIALS AND METHODS

We conducted a cross-sectional study in a gastroenterology institution in Medellín, Colombia, between February and July 2020. It included all outpatients over 18 years of age admitted for a complete colonoscopy, administering an

informed consent form prior to the procedure. We built an Excel database from the following variables: Age, sex, colonoscopy equipment used, procedure indication, examination scope, Boston scale assessment, the physician performing the examination, and endoscopic and histological results. Data were collected from colonoscopy and pathology reports.

Seven gastroenterologists performed 1,001 colonoscopies in the study period, while an anesthesiologist or sedation physician, as appropriate, was responsible for sedation. Two pathologists with specific training in gastrointestinal histopathology provided the histopathological interpretation.

The colonoscopes used are of high definition: Some with LCI light filters used for detecting adenomas and with BLI filters and magnification to characterize lesions; others with NBI filters also used for characterization.

We verified the cecal intubation rate in each colonoscopy report and estimated the reach to the cecum and terminal ileum. The withdrawal time of the colonoscope from the cecum was six minutes for all cases, following the institutional protocol. The effectiveness of colon cleansing was classified using the Boston scale, which assessed the fecal presence and visibility of the colon in its three segments. Those studies without a record of the Boston scale were treated as missing data.

The ADR was calculated from the proportion of patients with at least one visualized mucosal adenoma. We obtained the histological type of each adenoma and its location by a segment of the colon. Reports of non-adenomatous polyps were excluded from the analysis, as were those studies in which it was not possible to reach the cecum.

The institutional ethics committee approved the conduct of the study, considering it to be of minimal risk since the estimation of the statistics concerned does not constitute an intervention or experiment. This study also contemplates the fundamental principles of research ethics under the Declaration of Helsinki, version 2013⁽¹¹⁾, and Resolution 008430/1993 issued by the Colombia Ministry of Health⁽¹²⁾.

Statistical analysis

We analyzed the data using Excel, version 2019, and Jamovi, version 1.2.25. The adenoma detection rate was calculated for the entire cohort and then for the main examination indications.

Univariate analysis was performed by determining absolute and relative frequencies for qualitative variables. We used the mean and standard deviation (*SD*) as quantitative variables after verifying the assumption of normality. The Chi-square association test was employed for independent

samples, and the Odds Ratio (*OR*) was estimated with its respective 95% confidence interval (95% *CI*). We considered a statistically significant *p*-value < 0.05.

A logistic regression model was established to identify the variables that can be considered predictors for detecting adenomas in patients undergoing colonoscopy.

The dependent variable in the model was the detection of adenomas (categorical, yes/no). We made two predictive models: The first only included colonoscopy indications, which were significant in the bivariate analysis (*p* < 0.05). The second additionally gathered demographic variables of interest to the research group. Finally, the model with the best statistical fit was accepted.

RESULTS

We identified 992 eligible patients out of 1,001 patients undergoing colonoscopy between February and July 2020; the nine patients excluded are due to incomplete studies. Sixty-one percent of the population was female, and the average age was 52 years (*SD* 14).

The examination reach to the terminal ileum was obtained in 934 patients and the cecum in 52 for a 99% optimal reach. Colon preparation was assessed using the Boston scale, considering a score ≥ 2 in each segment satisfactory. Eighty-eight percent of the patients were adequately prepared; in 2%, we did not obtain the scale assessment, regarded as missing data in the analysis. No statistically significant differences were found in the detection of adenomas according to the Boston scale (*OR* 0.97; 95% *CI* 0.59-1.60; *p* 0.913).

Adenomas were detected in 208 patients (21%), of which 175 were older than 50 years (84%), and 25 patients (12%) were in the age range of 40–49 years (**Table 1**). When analyzing the presence of adenomas by sex, the ADR in men (28%) was higher than in women (17%), a statistically significant difference (*OR* 1.92; 95% *CI* 1.41-2.62, *p* < 0.001).

Table 1. Detection of adenomas by age range

Age groups	Number of colonoscopies	Number of patients with adenomas	ADR (%)
< 40	208	8	4 %
40-49	160	25	12 %
50-59	289	70	33 %
60-69	214	60	29 %
70-79	96	33	16 %
> 80	25	12	6 %
Total	992	208	100 %

The examination indication variable was categorized into five primary causes. The adenoma detection results were positive fecal occult blood (43%), personal history of polyps in the colon (35%), screening in an average-risk population (aged 50 years with no history) (25%), family history of CRC (13%), and patients under 50 (diagnosis of gastrointestinal symptoms) (9%).

The variables with a statistical significance of $p < 0.05$ in the bivariate analysis were entered into the logistic regression model (**Table 2**).

Table 2. Bivariate analysis to detect adenomas

Variable	p	OR	95% CI	
			Lower	Higher
> 50 years	<0.001	3.96	2.66	5.89
> 40 years	<0.001	8.56	4.15	17.7
Male sex	<0.001	1.92	1.41	2.62
Use of LCI filters	0.002	1.66	1.21	2.29
Positive PH of polyps	<0.001	2.38	1.63	3.50
Positive FOB	0.007	3.00	1.29	6.93
Family history of CRC	0.262	0.550	0.190	1.59
Boston scale	0.913	0.973	0.590	1.60

PH: Personal history; CRR: Colorectal cancer; CI: Confidence interval; LCI: Linked color imaging; FOB: Fecal occult blood

The variables that predict the detection of adenomas according to the logistic regression model are sex, age >40 years, colonoscopy LCI filters, fecal occult blood, and personal history of polyps (**Table 3**).

Table 3. Logistic regression model to detect adenomas

Variable	Coefficient	p	OR	95% CI	
				Lower	Higher
Intercept	-0.923	0.059	0.397	0.152	1.04
Male sex	0.548	<0.001	1.730	1.256	2.38
> 40 years	1.962	<0.001	7.114	3.427	14.77
Positive PH of polyps	0.625	0.002	1.869	1.255	2.78
Positive FOB	0.983	0.026	2.673	1.126	6.35
Use of LCI filters	0.360	0.036	1.433	1.024	2.00

PH: Personal history; CI: Confidence interval; LCI: Linked color imaging; FOB: Fecal occult blood.

When analyzing the results of the logistic regression model, the variable that best explains the probability of detecting adenomas is being over 40 years old, with an OR of 7.11. Men are 1.7 times more at risk than women. Individuals with a personal history of polyps are 1.86 times more likely to have adenomas than those without them. The positive fecal occult blood significantly increases the risk of adenomas with an OR of 2.67. Finally, using LCI filters increases detection likelihood 1.43 times than not using them.

DISCUSSION

Colonoscopy is considered the gold standard for CRC detection. Various indicators assess pre-, intra-, and post-procedural quality^(3,13). One of them is the ADR, defined as the proportion of screening colonoscopies with at least one identified adenoma⁽¹⁴⁾. The importance of its measurement lies in that as the ADR increases by 1%, the risk of CRC decreases by 3% and mortality by 5%^(4,14,15), strongly related to the prevention of interval cancer⁽¹⁶⁾. Colonoscopy screening and early detection of precursor lesions through polypectomy have proven highly effective in preventing CRC and its mortality rates. Therefore, it is a general objective to improve the results of these indicators^(1,17,18) and define appropriate follow-up periods.

The overall result of detecting adenomas in our population was 21%. However, it is crucial to analyze this behavior according to the most frequent colonoscopy indications: Screening, diagnosis, and surveillance⁽¹⁹⁾.

Firstly, for the average risk population⁽²⁰⁾, the expected result is to detect adenomas in 25% of cases^(4,21). The primary objective of CRC screening is to identify the disease in early states and locate precancerous lesions in individuals who do not have a history of CRC or polyps⁽²²⁾. In our screening population, understood as that population undergoing colonoscopy without additional risk factors for CRC, except for age over 50 years, the ADR identified was 25%, consistent with the reported detection goals for this population.

Like other studies, the male gender⁽²³⁾ and being over 40 years old^(7,22) were statistically significant risk factors for detecting adenomas. In stratifying the population by age range, this study found that 12% of patients with adenomatous polyps were between 40 and 49 years old (average age of 44 years). Given this finding, adenoma detection was compared from the age of 40 with those older than 50, resulting in a higher detection likelihood from the age of 40 (**Table 2**). The initiation of screening in patients with average risk has been shortening, approaching 45 years old in some studies^(7,22). Data on the prevalence of adenomas between 40 and 49 years of age of up to 5% have been reported⁽²⁴⁾. These results are of utmost clinical importance in our environment since they suggest starting the detec-

tion of adenomas ten years earlier than recommended in current practice.

Regarding risk factors, it is widely known that people with a history of CRC in first-degree relatives have twice the risk as to the general population^(25,26), probably due to a combination of genetic and environmental factors⁽²⁷⁾. Three percent of the patients had this history; however, it was not a predictive factor for detecting adenomas owing to the low representativeness within the population studied.

Other quality indicators for a colonoscopy that determine good detection results are the examination reach to the cecum and adequate cleansing of the intestinal mucosa. A complete assessment was achieved in 99% of the examinations, mainly to the terminal ileum, allowing evaluation of the mucosa during withdrawal. Nonetheless, the comprehensive assessment does not ensure an adequate view since it depends on the degree of preparation of the colon prior to the examination and intraprocedural techniques, such as suitable cleansing and suction, distension of the colon, and inspection of all folds⁽²⁸⁾. The level of cleanliness and visibility of the mucosa was assessed with the Boston scale, which favors objective and standardized results⁽⁴⁾. Inadequate preparations, with a 0–1 score in any segment, are associated with an increased risk of missed adenomas^(4,29,30); therefore, the goal is to obtain preparations with 2–3 scores. Despite being indicators of great importance, the reach of the examination and the preparation results were not significant variables to predict adenomas in the logistic regression model in this study.

It is described that no screening test reaches the sensitivity of colonoscopy in detecting precancerous colon lesions, being four times higher than the fecal immunochemical test (FIT), which is the closest one⁽³¹⁾ and one of the most used for screening around the world⁽³²⁾. Patients who undergo colonoscopy with a positive FIT result have a higher prevalence of CRC and higher ADR than a screening colonoscopy⁽³³⁾. In our environment, FIT is not routinely used as a screening test; however, fecal occult blood (FOB) is frequently observed as an indication for colonoscopy. In cases with positive results, the FOB was more likely to detect adenomas (OR 2.67; 95% CI 1.12–6.353), which is deemed a significant predictor.

Another intervention to prevent CRC is polypectomy. It reduces the risk of death from CRC in the first ten years

after the performance to a level similar to patients without adenomas⁽⁵⁾. The procedure evaluates the malignant potential of any discovered polyp based on the macroscopic and microscopic characteristics of malignancy, such as surface appearance, vascularization, induration, ulceration, polyp size, villus histology, high-grade dysplasia, among others⁽³⁴⁾. In our population, a personal history of polyps represented a probability of detecting adenomas 1.86 times higher than those without the history, being a relevant predictor that allows intervention in CRC prevention with polypectomy and suggests that patients with such a condition are candidates for a CRC precursor lesion surveillance program.

Lastly, imaging quality in colonoscopy through devices or techniques⁽³⁵⁾ is one of the objectives set to reduce the proportion of missed adenomas and impacts the prevention of recurrent adenomas and CRC⁽³⁶⁾. Advanced endoscopic imaging technology that emphasizes mucosal color changes (LCI) and vital colorations and provides clearer and brighter images (high definition)⁽³⁷⁾ should be employed both for screening the average risk population and for CRC precursor lesion surveillance programs, considering the superiority of the image compared to conventional white light^(38–40). However, this imaging does not control the so-called recognition errors or those related to the observer's attention and view^(39,41).

Given the epidemiological and nutritional transition of the population in recent years, this study discusses reducing the starting age for CRC screening. It lists those indications for a colonoscopy that are predictors for finding adenomas.

CONCLUSIONS

The indications for colonoscopy can predict the probability of detecting adenomas. Male gender, a personal history of polyps, the presence of occult blood in feces, and the search for adenomas after the age of 40 are the variables that increase the probability of finding adenomas. The use of LCI filters increases the detection of lesions. The suggested age to start CRC screening is 40 years.

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Characteristics of Inflammatory Bowel Disease Compared to Other National Centers in Colombia

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Abstract

Introduction: Inflammatory bowel disease (IBD) is an immune-mediated disease whose incidence in Latin America has increased in recent years. **Aim:** To analyze the demographic and clinical characteristics of patients with IBD treated in a university hospital and present the epidemiological data compared to other centers in Colombia. **Patients and methods:** Descriptive study of patients with IBD (1996-2019) at the Hospital Universitario Fundación Santa Fe de Bogotá. Analysis of data from centers in Medellín, Cali, Bogotá, and Cartagena. **Results:** Of 386 patients, 277 presented with ulcerative colitis (UC), 102 with Crohn's disease (CD), and seven with unclassifiable colitis. IBD was more frequent in women (53%). Mortality was less than 1%. The involvement of UC was mainly pancolitis (42.6%). The greater the extent of the disease, the higher the hospitalization and surgery rates ($OR\ 3.70, P < 0.01$). Thirteen percent of patients with UC received biologics. Compromise due to CD was mainly ileocolonic (43.6%) and ileal (43.6%). The predominant clinical pattern of CD was structuring (50%). Forty-five percent received biologics and 56% surgery. Primary sclerosing cholangitis (PSC) was found in 4% of patients ($n = 15$). Two patients with PSC developed colorectal cancer ($OR\ 4.18; p\ 0.008$), while 13 patients with UC developed colon cancer and seven dysplastic changes. Three patients with CD developed colon cancer. **Conclusions:** The results were compared to other reference centers. We found similar trends in the clinical behavior and treatment of IBD, with higher hospitalization and surgery rates in our cases.

Keywords

Inflammatory bowel disease, Colombia, ulcerative colitis, Crohn's disease, phenotype.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a cause of immune-mediated disease. They are characterized as chronic diseases with high morbidity, which can significantly impact the survival and quality of life of the patient and their family and entail a high cost for the health system⁽¹⁾.

Therefore, the efforts to establish an adequate diagnosis and appropriate treatment by improving patients' quality of life motivated the research on this pathology. Since its pathophysiology is multifactorial, including environmental, genetic, and immunological factors, it is crucial to know the behavior of the disease in different world populations⁽¹⁾.

IBD is most often diagnosed between 15 and 30 years of age; however, there is a second incidence peak between

50 and 70⁽²⁾. It is a disease with a higher prevalence in Caucasians and developed countries. Despite this, in the last two decades, epidemiological studies have shown a rapid increase in IBD incidence in countries in the Middle East, Asia, and South America⁽³⁾. Some studies show a decrease in IBD in North America⁽⁴⁾, while IBD incidence has increased significantly in Latin America in the last 21 years⁽⁵⁾.

The frequency of IBD has increased recently in Colombia. A study based on the Integrated Colombian Health Information System (SISPRO) for 2018 estimated the prevalence at 5.85 for CD and 51.77 for UC per 100,000 inhabitants⁽⁶⁾.

This study intends to describe and discuss the demographic and clinical characteristics of patients with IBD whom the multidisciplinary group treated at the Hospital Universitario de la Fundación Santa Fe de Bogotá. As a secondary objective, we want to compare the experience reported by a medical center in Cartagena and some reference centers in Medellín, Cali, and Bogotá.

Studying the epidemiological behavior of IBD aims to delve into the association of the pathology with risk factors and its particular clinical characteristics, which is of paramount importance since risk factors may differ according to each population's culture, demographics, diet, health services, infrastructure, and socioeconomic status.

PATIENTS AND METHODS

We conducted a descriptive retrospective study by collecting information from the medical records of patients diagnosed with IBD at the Hospital Universitario de la Fundación Santa Fe de Bogotá (FSFB) between 1996 and 2019. IBD diagnostic criteria followed the guidelines of the ECCO evidence-based consensus and the American College of Gastroenterology (ACG)⁽⁷⁻⁹⁾. Data were tabulated according to diagnosis, demographics, and clinical data. According to the colonoscopy findings, severity and extension were determined under the Montreal classification⁽¹⁰⁾.

We performed a descriptive statistical analysis and compared proportions with adequate confidence levels. Finally, a comparison was made with prevalence studies published in Colombia. The FSFB ethics committee approved the study protocol under registration CCES 8686-2017.

RESULTS

General characteristics of patients

Three hundred eighty-six patients who met the diagnostic criteria between 1996 and 2019 were included. Of these, 277 had a diagnosis of UC, 102 of CD, and seven of unclassifiable colitis (2%). A predominance of UC over CD was

found, with a 2.7:1 ratio. The average age of diagnosis for UC was 42 years (range 7-91) and 47 years for CD (range 12-86), their difference being statistically significant (p 0.002). IBD was diagnosed more frequently in women than men; however, it was not statistically significant (p 0.44). The average follow-up of patients was 41.87 months for CD and 50 months for UC. UC hospitalization rate was 47% compared to 83.2% for CD.

Demographic characteristics, frequency of hospitalization, and mortality for each pathology are presented in **Table 1**.

Table 1. Demographic characteristics of patients with IBD at the Hospital Universitario Santa Fe de Bogotá, Colombia

Number of patients (<i>n</i> = 379)	Ulcerative colitis (<i>n</i> = 277)	Crohn's disease (<i>n</i> = 102)	Fisher's <i>p</i>	OR
Median diagnostic age (range): Years	42 (7-91)	47 (12-86)	0.02	-
Sex			0.244	1.33
- Male	132 (47.7 %)	41 (40.6 %)		
- Female	145 (52.3 %)	60 (59.4 %)		
Hospitalization	130 (47 %)	83 (82 %)	0.00	5.42
Mortality	2	1	ND	ND
Surgery	29	42		

NA: Not available.

Clinical features

Pancolitis was the most frequent manifestation of UC (n = 118; 46.8%). We found that 14.8% of the patients were in clinical remission, 21.64% with moderate disease, 28.73% mild, and 35.45% severe. In CD, the most frequent location of the disease was the ileum and the ileocecal junction, 44 patients in each segment (43.6%), respectively, while isolated colonic involvement was identified in 13 patients (12.9%) (**Table 2**). Twenty-three patients with CD (22.5%) had perianal and anal involvement, and no patient had upper digestive tract involvement above the ligament of Treitz. The most common phenotype of patients with CD was type B2 stenosing (49.5%), while type B1 and B3 were found in a lesser proportion (**Table 2**).

Hospitalizations and comorbidities

In our series, 213 (55%) patients were hospitalized; the majority had a diagnosis of CD (61%) when compared with patients with UC (OR = 0.18, CI 0.01-0.38, p 0.001). Of the 130 patients with UC admitted to the hospital,

62.39% had extensive involvement of the disease (OR = 3.28, CI 1.99-5.41, p 0.001). Patients with UC with rectal involvement (proctitis) had a hospitalization rate of 26.67% and 43.75% in patients with left-sided colitis. It was Of all the patients with CD, those who most frequently required hospitalization were patients with the stenosing B2 phenotype (20.4%), followed by the penetrating B3 phenotype (10.6%) and, less frequently, the non-stenosing and inflammatory B1 (8.3%).

Among the diseases associated with IBD, primary sclerosing cholangitis (PSC) was found in 14 patients (3.6%) of 386. Of these, eight were women, and six were men. Most had a diagnosis of UC (93.3%), 13 patients had severe extensive colitis, and one patient had severe left-sided colitis. One patient with PSC had a diagnosis of CD, with ileocolic extension and stenosing behavior.

The average age at the time of PSC diagnosis was 56.28 years. Of all patients with IBD who had PSC, two (14.3%) developed colorectal cancer. Compared to patients who did not have PSC, only 3.8% developed colorectal cancer. A positive association was obtained between PSC and colorectal cancer in patients with IBD, with an OR of 4.18 (p 0.008), which was statistically significant.

In the group of patients with UC, colon cancer was reported in 14 (4.3%), low-grade dysplasia in six (2.2%), and high-grade in one (0.4%); additionally, three patients with CD (2.9%) developed colon cancer.

Table 2. Extent, location, and behavior of IBD (Montreal classification)

	Ulcerative colitis ($n = 277$)	Crohn's disease ($n = 102$)
- E1: Ulcerative proctitis	99 (35.7 %)	NA
- E2: Left-sided colitis	60 (21.7 %)	NA
- E3: Extensive ulcerative colitis (pancolitis)	118 (42.6 %)	NA
CD location		
- L1: Ileal	NA	44 (43.6 %)
- L2: Colonic	NA	13 (12.9 %)
- L3: Ileocolonic	NA	44 (43.6 %)
- L4: Upper gastrointestinal	NA	0 (0 %)
CD behavior		
- B1: Nonpenetrating/inflammatory	NA	28 (27.7 %)
- B2: Stenosing	NA	50 (49.5 %)
- B3: Penetrating	NA	23 (22.8 %)
- Existence of perianal disease	NA	23 (22.8 %)

NA: Not applicable.

Medical treatment

In the group of patients with UC, 264 received treatment with 5-aminosalicylates (5-ASA) (94%), 163 with steroids (57%), 88 with azathioprine (30%), and 38 with biological therapy (13%). Initially, of the 38 patients with an indication to start biological treatment, 50% received adalimumab. Besides, 47% started treatment with infliximab and 3% with golimumab. Ten of the 38 patients (26%) required second-line treatment with vedolizumab, infliximab, and adalimumab. Later, one patient required third-line biologic therapy with golimumab.

In the group of patients with CD, 70 patients received medical management with 5-ASA (69.3%), 66 with steroids (65.3%), 48 with biological therapy (47.5%), and 39 with azathioprine (38.6%). Of the 48 patients who required management with biologics, adalimumab was most frequently used as first line ($n = 32$, 31.7%), followed by infliximab ($n = 15$, 14.9%) and vedolizumab ($n = 1$; 1%). Moreover, 23 patients required second-line biological treatment with adalimumab ($n = 8$, 7.9%), vedolizumab ($n = 2$, 2%), and ustekinumab ($n = 1$, 1%), and one patient received golimumab. Then, four patients required a third-line biologic with vedolizumab and one patient with certolizumab.

Surgical treatment of patients with UC

Regarding surgical treatment, 102 patients with inflammatory disease required surgical treatment. Of these, 45 had a diagnosis of UC (44.1%), and the main indication was resistance to medical management. Most of the operated UC patients had an extensive disease or pancolitis (OR 3.70, CI 1.83-7.50, $p < 0.01$).

UC with abdominal surgery in IBD (not liver transplant)

Of the 45 UC patients who underwent colectomy, 29 underwent surgery at the FSFB, 16 (55.2%) were women, and 13 (44.8%) were men. The most common procedure was abdominal proctocolectomy with ileoanal anastomosis (58.6%) (Table 3). The need for abdominoperineal resection in patients with ulcerative colitis is rare; however, it was necessary for two patients, one with rectal cancer and invasion of the sphincter complex and the other with severe anal stenosis. The average age at diagnosis was 42.24 years (deviation of 18.4 years), ranging between eight and 70 years. The average age of the patients who underwent abdominal surgery was 50.34 years (deviation of 16.79 years), ranging between 16 and 77 years. The average time between IBD diagnosis and abdominal surgery was 8.1 years (deviation of 8.47 years), ranging between one and 37 years.

Surgical treatment of patients with CD

In this case, 57 patients had a diagnosis of CD (55.9%); the main surgical indication was perianal complications. Of this group of patients, the majority had ileocolonic involvement ($n = 31$; 54%), 31.6% had ileal involvement ($n = 18$), and 14% had colonic involvement ($n = 8$). Fifty-six percent of operated CD patients had a stenosing phenotype ($n = 32$; OR 0.86; CI 0.86-1.88; P 0.290), 36.8% penetrating type ($n = 21$; P 0.011), and 7% inflammatory involvement ($n = 4$, OR 0.15, CI 0.05-0.39, $p < 0.001$).

CD with perianal treatment

Of the 57 patients with CD, 13 received surgical treatment for the perianal disease at the FSFB, the most frequent indication, of whom eight (61.5%) were men (Table 3). Of the patients operated at the FSFB with a perianal surgical procedure, the age at the time of diagnosis was 28.7 years (SD 13.7 years), ranging from 12 to 65 years. The

average time between IBD diagnosis and the first perianal surgery was 4.5 years, ranging between one and nine years. Patients required 1.58 reinterventions (range zero to ten, maximum ten). At the surgery, 10/13 received biological therapy, 10/13 steroids, 9/13 5-ASA, and 5/13 azathioprine.

CD with abdominal surgery

Of the 57 CD patients who required surgery, 29 underwent abdominal surgery at the FSFB; 19 (65.5%) were women, and ten (34.5%) were men. The main indication for surgery was intestinal obstruction due to intestinal stenosis, secondary to CD (Table 3). At the time of diagnosis, the average age was 57.2 years (deviation of 18.1 years), ranging from 14 to 86 years. During the abdominal surgery, the average age was 61.4 years (deviation of 16.98 years), going between 14 and 86 years. The average number of years between IBD diagnosis and abdominal surgery was 4.24 years, ranging from zero to 31 years.

Table 3. Characteristics of patients with IBD who received surgical treatment at the Hospital Universitario Fundación Santa Fe de Bogotá

	Surgical indication, n (%)	Procedure, n (%)
UC ($n = 29$)	Resistance to medical treatment 17 (58.6%)	Abdominal proctocolectomy with ileoanal anastomosis 18 (62.1%)
	Colon cancer 4 (13.8%)	Subtotal colectomy with rectal preservation 7 (24.13%)
	Perforation or toxic colitis 6 (20.7%)	Segmental colectomy + Hartmann's operation 2 (6.9%)
	Rectal cancer/Anal stricture 1 (3.4%)/1 (3.4%)	Abdominopelvic resection 2 (6.9%)
CD perianal surgery (42)		
Perianal surgery ($n = 13$)	Perianal surgery: Fistula/Abscess 13 (100%)	Fistulectomy with seton placement 7 (53.8%)
		Abscess drainage 6 (46.1%)
Abdominal surgery ($n = 29$)	Obstruction/Stenosis 26 (89.6%)	Right ileocelectomy 14 (48.3%)
	Colorectal cancer 3 (6.7%)	Isolated right hemicolectomy 12 (37.9%)
		Left hemicolectomy 1 (3.4%)
	Rectovaginal fistula 1 (3.4%)	Abdominopelvic resection 2 (6.7%)

UC: Ulcerative colitis; CD: Crohn's disease.

Of the patients who received surgical management, three had colorectal cancer (one moderately differentiated rectal adenocarcinoma, one adenocarcinoma of the right colon, and one small intestine cancer), and one patient had a serrated adenoma of the cecal appendix. **Table 3** is a description of the surgeries at the FSFB.

Results compared to other national groups

Table 4 compares the characteristics of patients with IBD from the different reference centers in Colombia, in cities such as Medellín, Cali, and Bogotá⁽¹¹⁻¹³⁾. The number of patients reported in the different studies varies between 165 and 649. Our institution has a number of patients similar to the other reference groups. The behavior and location of the disease are similar, with pancolitis being reported more frequently in Medellín and Bogotá (FSFB). The age of manifestation is similar, with an average of 40.7 years in the four studies. Of note is that we observed more hospitalizations and surgeries in our group.

In addition, we compared our data with an IBD prevalence study in Cartagena, Colombia⁽¹⁴⁾. This study found 26 patients with IBD out of 90,932 patients in the database in a review until 2006. The most frequent diagnosis in the

Cartagena study population was UC ($n = 20$), as in the other reference centers in Colombia and the FSFB. IBD prevalence was higher in females, as noted in our institution⁽¹⁴⁾.

DISCUSSION

Understanding the differences in IBD manifestation between the various geographical regions is vital due to the disease's burden on health systems and to devise the appropriate prevention and treatment strategies. The incidence and prevalence in developing countries are constantly increasing and have been attributed to the population's rapid Westernization⁽⁵⁾. Colombia is part of the Latin American countries with a significant increase in prevalence and incidence⁽⁶⁾. This study presents 386 patients treated for 23 years.

In our study, UC was diagnosed more frequently than CD, as reported in the other four national studies⁽¹¹⁻¹⁴⁾. It was also found that the average age for diagnosis of UC and CD was 42 and 46 years, respectively, as informed by other reference centers in the country and international reviews^(2,15,16).

In the present study, IBD was more frequent in women. As in other national studies, UC is predominantly female⁽¹²⁻¹⁴⁾. The same trend applies nationwide to CD,

Table 4. Characteristics of patients with IBD between reference centers in Colombia

	Hospital Pablo Tobón Uribe, Medellín (2001-2017)	Fundación Clínica Valle de Lili, Cali (2011-2015)	Fundación Clínica Colombia, Bogotá (2013-2016)	Hospital Universitario Fundación Santa Fe de Bogotá (1996-2019)
Number of patients	649	416	165	386
UC/CD	3/1	2.6/1	3.1/1	2.7/1
Mean age UC/CD (years)	39.9/41	42/43	39/44	42/46
UC extension (%) rectal/left/extensive	24/32/43	53/20/27	20/32/46	37/22/39
CD location (%) ileum/colon/ileocolonic	37/21/37	54/33/13	35/12/52	44/13/44
CD behavior (%) inflammatory/stenosing/penetrating	37/21/19	49/20/29	60/32/2.5	28/50/23
UC surgery (%)	12	9	5	29
CD surgery (%)	39	46	27	42
CD hospitalization (%)	69	52	ND	83
UC hospitalization (%)	55	49	ND	47
Treatment				
- ASA/AZA/STE/BIO UC (%)	94/41/55/21	84/24/32/15	82/23/70/16	94/30/57/14
- ASA/AZA/EST/BIO CD (%)	37/57/66/46	12/29/20/32	30/35/35/35	66/40/66/47

ASA: 5-aminosalicylates; AZA: Azathioprine; UC: Ulcerative colitis; CD: Crohn's disease; STE: Steroids; BIO: Biological therapy; NA: Not available.

except in Medellín, where a higher proportion of men was described⁽¹¹⁾. The impact of gender on the course of IBD has been a controversial topic in international studies⁽¹⁷⁾. The female gender has been associated with a higher rate of long-term complications in ileoanal pouch anastomosis, such as pouchitis, intestinal obstruction, fistula, and pouch failure⁽¹⁸⁾. Future studies will analyze whether female patients have more long-term complications after surgical treatment.

In our series, a significant hospitalization rate was noted in patients with extensive UC or pancolitis. The extent of the disease was found to be a significant risk factor in patients with UC.

Some risk factors have been described that may determine the need for hospitalization in patients with UC. One study found that patients with extensive UC have a higher risk of hospitalization within the first 90 days of diagnosis (approximately 60%). The need to use corticosteroids early is a statistically significant predictive factor and translates into higher hospitalization rates. In contrast, gender, age at diagnosis, and time of disease evolution were not significantly associated with the first hospitalization of a patient with UC⁽¹⁹⁾. Another study found that the use of biological therapy and the elevation of C-reactive protein are predictive factors about the length of hospital stay, while the activity of the disease is more related to the number of outpatient consultations⁽²⁰⁾.

Similarly, patients with stenosing-type CD and perianal complications have higher hospitalization rates. These results are related to predictors described in other studies, including the presence of fistula, the use of biological therapy, and the severity of disease activity. Age, sex, use of steroids, and biological therapy are predictors of the number of outpatient visits⁽²⁰⁾.

Phenotypic characteristics were reported in our study, and we found that in CD, ileal and ileocolic extensions were the most frequent. Only 13% of the patients in this study had colon involvement, like the other center in Bogotá (12%)⁽¹³⁾. In other cities, such as Medellín and Cali, colon involvement was mostly reported^(11,12). More studies are needed that include the extension of the disease as a variant since it could be speculated that it may be related to cultural differences, habits, and diet between regions, including genetic characteristics and their microbiome in cities.

A systematic review that studied the phenotypic characteristics of UC and CD in South America and the Caribbean reported that ileocolonic extension (L3) was the most frequent in these regions⁽²¹⁾. This same study showed that the extent of the disease in UC varies between countries in Latin America. For example, no distal proctitis (Montreal E1 classification) cases were detected in Brazil, but up to 55.35% were found in Puerto Rico. Left-sided colitis's invol-

vement varies between 11.1% and 62.9% in Peru. Pancolitis (Montreal E3 classification) was found in 12% in Brazil and 77% in Argentina⁽²¹⁾. In the present study, there is a slight variation in the extension of UC in Colombia. The location near the rectum and the extensive involvement of the disease were more frequent than the involvement of the left colon, as published in other studies nationally⁽¹¹⁻¹³⁾.

There is a significant association between IBD and PSC. Globally, it is reported that 50-80% of patients with PSC simultaneously have IBD, pancolitis being more common in UC^(21,22). As an extraintestinal manifestation of IBD, PSC has been described as a disease with a particular PSC-IBD phenotype⁽²³⁾. It is estimated that approximately 70% of patients with PSC have underlying IBD, most often UC. Five percent of patients with UC develop PSC during their disease⁽²⁴⁾.

Our results are consistent with these statistics: 4% of IBD patients developed PSC, of which two also had colorectal cancer. Specifically, we present a significant association between PSC and colorectal cancer in the present study, with an OR of 4.18. The combination of IBD and PSC significantly increases the risk of colorectal and hepatobiliary malignancy⁽²⁵⁾.

It has been established that chronic inflammatory changes predispose to changes in the mucosa, which can evolve and create a neoplasm⁽²⁶⁾. The most significant risk occurs after the first ten years of the disease (0.5-1.5% per year)⁽¹⁵⁾. The PSC-IBD phenotype has been described as more inactive and asymptomatic; nonetheless, it is related to a more significant progression of low-grade dysplastic changes to advanced colorectal neoplasms^(24,27). Considering that many patients in Colombia with extensive UC are at risk of developing PSC, close clinical surveillance is vital, supported by radiological and endoscopic studies.

Colon cancer was significantly reported in our study. These results are relevant given that international studies have reported a prevalence of 3.7% of colorectal cancer in patients with UC⁽²⁸⁾. Worldwide, a significant decrease in the incidence of colorectal cancer in patients with IBD has been reported, which is due to successful surveillance and screening programs and the better control of mucosal inflammation, that is, an adequate treatment⁽⁶⁾. The risk factors associated with colorectal cancer in this population include the time of evolution, the extent, severity of the disease, the presence of inflammatory pseudopolyps, coexisting PSC, and family history of colorectal cancer⁽²⁹⁾.

The main objective of IBD management is to obtain clinical remission and maintain it with the treatment that has the lowest risk of potential side effects⁽³⁰⁾.

New biological therapies have been developed for refractory or severe diseases, considering the high failure rate with conventional treatment⁽³¹⁾. Consequently, the use of biological therapy has increased in Colombia. Studies have shown

that up to 18.5% of patients with UC receive biological therapy, with infliximab and adalimumab being the first line⁽⁶⁾.

Furthermore, 5-ASAs continue to be the mainstay of treatment in UC. We reported that 94% of patients with UC received this drug in our results. However, the use of biological therapy is increasing in our institution. Similar results were observed in the national studies above.

Surgical treatment in patients with CD has been reported in around 27.6% and 6.7% of patients with UC⁽⁶⁾. Our study found a higher number of surgical events in patients diagnosed with CD than in patients with UC. When comparing these results with those of other reference centers, our institution had a higher number of surgical events, which can be explained by the severity of the disease, dysplastic lesions in the colon, and associated perianal complications.

Being refractory to medical treatment or adverse reactions was the main indication for surgical treatment in UC, requiring a proctocolectomy with ileoanal anastomosis and ileal J-pouch. We found that the association between surgical treatment and disease extension was statistically significant in our series. Thus, the more extensive the involvement, the higher the likelihood of requiring surgical treatment. The literature reported that 20% of patients with UC, and up to 80% of patients with CD, require surgery in the course of their disease. In patients with UC, proctocolectomy is the surgery of choice with a curative objective, while ileoanal anastomosis plus the construction of an ileal pouch replaced permanent ileostomy, which has improved patients' quality of life^(32,33).

Surgeries in CD are not curative, and their objective is to treat the intestinal and perianal complications of the disease⁽³³⁾. Severe complications of CD that require surgical treatment include obstruction, recurrent sub-obstructions, abdominal abscesses, perforation, bleeding, or cancer. The most common surgical procedure is ileocecal resection and primary reconstruction⁽³³⁾.

Strictureplasty is less frequently indicated in patients with proximal small bowel stricture⁽³³⁾. In a minority of cases, endoscopic dilations of the jejunum and ileum and more limited resections are also performed. However, these last procedures frequently have endoscopic recurrence one year after resection in up to 80% of patients, clinical recurrence in up to 20% of patients at two years, and 80% at 20 years⁽³³⁾.

In our experience, the most frequent surgical indications in patients with CD were perianal complications (abscesses, anal fistulas, and anal stenosis). The transmural inflammatory process of CD predisposes to the formation of anal fistulae, and the literature reports a 17-85% risk of perianal complications⁽³⁴⁾. Cohort studies have reported that 40-55% of CD patients older than ten years require surgery,

and 28% will require a second intervention in the following ten years^(34,35). When comparing our data, we found that the average time between the diagnosis of CD and the first perianal surgery was 4.5 years. Patients with CD may have intestinal obstruction secondary to intestinal stenosis (single or multiple). The mechanisms whereby these strictures develop include secondary inflammation caused by the disease, the scarring process, and the remodeling of the intestinal wall, transforming it into an inert tissue that loses its elasticity and ability to contract and produces strictures⁽³⁵⁾. In 28.4% of our patients with CD, it was necessary to perform an intestinal resection.

When presenting the phenotypic characteristics of IBD at the FSFB, compared to other reference centers in Colombia, we found similar results, mainly in the behavior and severity of the disease. The use of biological therapy has increased over the years. Also noteworthy is the increase in the number of surgeries in our institution, with the indication for surgery being that the patient is refractory to medical treatment and the complications of the disease. It is crucial to carry out more diverse population studies in Colombia in the future, identify the actual epidemiological profile of these pathologies in the country, and help plan health strategies with timely diagnoses.

LIMITATIONS

There is a selection bias in data collection because it is a retrospective study. The number of patients was lower than in the other reference centers when comparing the different follow-up times of the four groups. Considering this is a 23-year data collection study, IBD treatment has changed over time. Besides, we have pathological studies carried out outside the institution and verified by our specialists.

CONCLUSIONS

This retrospective study describes the characteristics of patients diagnosed with IBD who have been treated in the last two decades by a multidisciplinary group in a university hospital.

It should be noted that UC patients with extensive involvement of the disease have a higher incidence of associated complications, such as PSC and colorectal cancer. The stenosing behavior of CD was frequently found in our patients, as well as anal and perianal involvement, which required surgery. The results were compared to other reference centers. In comparing them, we identified the trends in clinical behavior and IBD treatment in the Colombian population.

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Surgical Management of Infected Pancreatic Necrosis. Case Series in a Quaternary Care Hospital in Bogotá, Colombia, 2014-2021

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Abstract

Introduction: Pancreatitis is a frequent pathology in our environment, mostly related to benign biliary pathology. It can progress to severe forms in 10-15% of cases, where the pancreatic tissue becomes necrotic and forms large collections with risk of infection. We do not have epidemiological data about the incidence or management of this complication in Colombia. **Aim:** This study aims to study the prevalence of infected pancreatic necrosis and describe the cases identified in a quaternary care hospital between 2014 and 2021. **Materials and methods:** A cross-sectional observational study. We analyzed records of patients diagnosed with stage 2 pancreatitis. Those cases with infected pancreatic necrosis that underwent debridement plus laparoscopic and open surgical drainage at Hospital Universitario Mayor Méderi in Bogotá, Colombia, between January 2014 and January 2021 were studied. A convenience sampling was carried out without calculating the sample size. We collected the patients' demographic and clinical variables, performing a descriptive statistical analysis in Excel. Qualitative variables were described through absolute and relative frequencies, while quantitative ones were expressed through measures of central tendency and dispersion based on their distribution. **Results:** We analyzed 1020 episodes of pancreatitis, finding pancreatic necrosis in 30 patients, i.e., a period prevalence of 2.9%. Of the patients, 83% ($n = 25$) underwent open drainage, with 48% ($n = 12$) mortality. About laparoscopic management, the reduction in postoperative organ failure was 40% ($n = 2$), with a 30% shorter hospital stay than the open drainage approach. Those patients with a level of procalcitonin (PCT) lower than 1.8 ng/mL had less mortality. **Conclusions:** The laparoscopic approach shows promising results regarding final morbidity and mortality.

Keywords

Pancreatitis, laparoscopy, procalcitonin, necrosis, APACHE.

INTRODUCTION

Pancreatitis has been defined on multiple occasions over the years. However, in 2013, it was defined as “an acute process of the pancreas, triggered by the inappropriate activation of pancreatic enzymes, with tissue injury, and local inflammatory response with variable involvement of other tissues or distant organ systems.”⁽¹⁾ Data in the United States report

more than 300,000 admissions per year for this pathology. Mortality does not exceed 1% in mild admissions, and this figure can increase to 30% in severe cases. Mortality in these patients is, to a greater extent, a consequence of multi-organ failure or complications related to the difficult control of the local inflammatory process⁽²⁾.

One of the secondary complications to the inflammatory process of the pancreas to be highlighted is infected pancre-

atic necrosis, which historically has a mortality that can reach 70% with surgical management (mainly open). However, since the advent of minimally invasive approaches (fine-needle aspiration, percutaneous, endoscopic, or laparoscopic drainage), this figure has decreased to 30%⁽³⁾.

In 2013, a study compared open with laparoscopic management for debridement of infected pancreatic necrosis. A reduction from 63% to 41% in the rate of postoperative complications with laparoscopic management was shown. Postoperative organ failure also reduced their rates from 54% to 22%. The postoperative intensive care unit (ICU) requirement decreased from 54% to 29%, while the incidence of post-operative fistulas was lower than in open management, decreasing from 36% to 10%⁽⁴⁾. This same study considered an adequate time for surgical management by laparoscopy. An average of 30 days was evaluated with better results in terms of mortality and morbidity after this time⁽⁴⁾.

What has been described above reflects the high morbidity rates of this pathology. This is why, in recent years, strategies for the prediction of pancreatitis complications, such as the measurement of serum procalcitonin, have been proposed. Multiple studies have shown its usefulness in assessing patients with suspected local complications like infected pancreatic necrosis, and it could also have a predictive value to consider antibiotic onset and its prognosis⁽⁵⁻⁸⁾.

It has been recently proposed that the safest management with lower rates of postoperative complications should be laparoscopic⁽⁵⁾. However, there are no epidemiological data in Colombia on the incidence of complications after pancreatitis or the management indicated for infected pancreatic necrosis. However, there are data reported in the literature where the low incidence of complications is exposed, which in some case series reaches up to 8%^(1,9). In recent years, thanks to greater surgeon training, the laparoscopic management of these pathologies has increased in our institution. This study will describe the experience in the surgical management of infected pancreatic necrosis at the Hospital Universitario Mayor Méderi in Bogotá, Colombia.

MATERIALS AND METHODS

A descriptive observational case series study was conducted. An initial medical history review of patients diagnosed with pancreatitis was performed. Then, in a second step, those patients who underwent surgical drainage of infected pancreatic necrosis between 2014 and 2021 were analyzed. Patients with pancreatitis of a different origin to the biliary one were excluded. Sample size calculation was not performed. All patients meeting the inclusion criteria were considered. Demographic, clinical, surgical, imaging, and paraclinical variables were collected. A descriptive analysis was carried out: qualitative variables were pre-

sented in absolute and relative frequencies, and quantitative variables were formulated with dispersion and central tendency measures according to normality.

Diagnosis of complication

Those patients who had torpid progression after the first 96 hours of comprehensive medical management were taken as suspects for a possible local complication of pancreatitis. Then, by performing imaging studies (abdomen tomography and abdominal magnetic resonance imaging), local complications were confirmed. Additionally, those patients who presented signs of systemic inflammatory response, sepsis, and radiological evidence of gas within the collection were considered infected. The diagnosis of infected pancreatic necrosis was then configured.

RESULTS

A total of 1020 medical records of patients diagnosed with acute pancreatitis were analyzed between 2014 and 2021. 33 patients who presented infected pancreatic necrosis as a major complication were identified and taken to surgical drainage by the institution's General Surgery service. Three patients were excluded, two of them due to traumatic pancreatitis and one because of secondary pancreatitis to hypertriglyceridemia.

A period prevalence of pancreatic necrosis of 2.9% was identified in relation to all pancreatitis analyzed. As for the population with infected pancreatic necrosis, most of them are male (70%; $n = 21$) with an average age of 56 years (**Table 1**). 93% of patients were studied preoperatively using an abdominal computed tomography with contrast. Antibiotic management prior to any intervention in all patients was initiated using multiple antibiotic therapies in 53% of them (**Table 2**). It is important to emphasize that in the ICU, antifungals were initiated prophylactically in 30% of patients, following institutional protocols adjusted to international scales of risk prediction for fungal colonization (isolating in 28% of patients). The entire sample that was subjected to surgical drainage was cultured from the collection. More than one germ was isolated in 33% of the evaluated samples, and in 26% of the cases, it was negative (**Table 3**).

In terms of invasive interventions for managing complications, it was found that, in all cases, patients were assessed by interventional radiology to perform interventions prior to surgical management. The open surgical approach was evidenced in 83% of cases, whereas 16% of cases were managed laparoscopically (**Figure 1**).

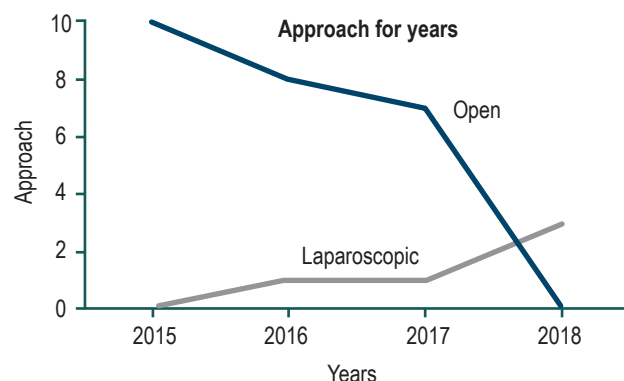
Regarding postoperative complications, 73% of patients ($n = 22$) did not present any. Out of 27% of patients with

Table 1. Comorbidities

Comorbidities	N	%
Denies comorbidities	13	34.2
Diabetes <i>mellitus</i> type 2	4	10.5
Chronic obstructive pulmonary disease	3	10.5
Chronic kidney disease	0	0
Arterial hypertension	7	18.4
Coronary disease	1	2.6
Immunosuppression	1	2.6
Others (peptic acid disease, hypothyroidism)	8	21.05
More than two comorbidities	7	23.3
Only one comorbidity	10	33.3

Table 2. Antibiotic therapy

Antibiotic	N	%
Meropenem	27	90
Ampicillin/sulbactam	3	10
Vancomycin	7	23.3
Caspofungin with fluconazole	9	30
Metronidazole	1	3.3
Monotherapy	14	46.6
Multiple therapies	16	53.3

**Figure 1.** Approach throughout the years.**Table 3.** Isolated microorganisms

Microorganism	N	%
<i>E. coli</i>	6	20
<i>P. aeruginosa</i>	2	6.6
<i>K. pneumoniae</i>	6	20
<i>K. oxytoca</i>	2	6.6
<i>E. faecalis</i>	2	6.6
<i>E. faecium</i>	4	13.3
<i>E. casseliflavus</i>	1	3.3
<i>E. gallinarum</i>	1	3.3
<i>A. baumannii</i>	2	6.6
<i>S. anginosus</i>	1	3.3
<i>S. epidermidis</i>	1	3.3
<i>S. haemolyticus</i>	1	3.3
<i>C. freundii</i>	1	3.3
<i>K. ascorbata</i>	1	3.3
<i>Candida albicans</i>	4	13.3
<i>Candida glabrata</i>	3	10
<i>Candida tropicalis</i>	1	3
Polibacterial	10	33.3
Bacterial with fungal	6	20
Monobacterial	6	20
Negative	8	26

complications, the most frequent condition was the pancreatic fistula. Postoperative outcomes such as reinterventions, total hospital stay, postoperative hospital stay in ICU, and mortality in those patients undergoing surgical management by laparoscopy are described in **Table 4**.

As part of an additional analysis, the use of procalcitonin was evaluated. We were able to observe that for values < 1.8 ng/dL, mortality was 8.33 (n = 1), compared with values > 1.8 ng/dL where it was 60% (n = 6). Its behavior is

Table 4. Postoperative variables

Approach	Mortality (n)	Hospital stay in an average of days (n)	Stay in POP intensive care unit in a maximum of days	Reinterventions (n)	Procalcitonin > 1,8
Open	25 (12)	2-132	0-65*	25 (19)	25 (8)
Laparoscopic	5 (0)	9-40	2-9	5 (0)	5 (2)

POP: Postoperative. *Day 0 for mortality.

described in **Table 5**. Additionally, as we do not have statistical data on this pathology in Latin America, we evaluated the institution's prevalence of infected pancreatic necrosis. In the 2014–2021 period, there were 1020 cases of pancreatitis (this data could be biased due to the institution's ICD-10 diagnostic records). Out of these, 30 patients presented infected pancreatic necrosis as a major complication of pancreatitis, equivalent to 2.9% of period prevalence. This is not far from what is described in the literature (1.2%).

Table 5. Paraclinical variables of patients with infected pancreatic necrosis

Paraclinical variable	N	%
Leukocytes		
- < 4000	0	0
- 4001-10 000	11	36
- 10 001-15 000	7	23
- 15 001-18 000	5	16
- > 18 000	7	23
Bilirubin		
- < 1.8	20	66
- 1.9-4.0	8	26
- > 4.9	2	6.6
Alkaline phosphatase		
- < 150	16	53
- 150-300	19	33
- > 300	4	13
Procalcitonin		
- < 1.8	12	40
- > 1.8	10	33
Not taken	8	26

DISCUSSION

The management of acute pancreatitis complications has steadily evolved for about 20 years. Initially, open management was perhaps the only approach. It showed morbidity rates ranging from 43% to 89% and mortality rates as high

as 39% in some case series. However, management through minimally invasive techniques has increased recently and showed better results in terms of morbidity and mortality compared to open management, such as in reinterventions (34% vs. 12%), pancreatic fistula (10% vs. 7%), mortality (18% vs. 27%) and hospital stay (40d vs. 49d), respectively, as reported in the literature⁽¹⁰⁻¹⁶⁾.

Additionally, the “step-by-step” management of infected pancreatic necrosis has been proposed. It establishes compliance with certain interventions in order to defer a surgical procedure that could add morbidity and even mortality to the patient⁽³⁾. In some case series, minimally invasive “step-by-step” management has demonstrated efficacy in about 40% of patients, reducing the need for surgical management⁽³⁾. 100% of our population was referred to the interventional radiology or gastroenterology service to assess the relevance of fine-needle aspiration, percutaneous drainage, or endoscopic drainage of the pancreatic lesion (following the “step-by-step” management of the infected pancreatic necrosis)⁽³⁾.

In 20% of cases, patients underwent percutaneous drainage of the lesion first, and 3% underwent fine-needle aspiration. The rest of our population required surgical management due to technical difficulties of the percutaneous/endoscopic procedure. We can evidence that percutaneous management was effective in 23% (n = 7) of our patients and prevented an eventual surgical procedure. This is not far from what was reported in the literature (35%–40%)⁽³⁾.

However, in surgical terms, the laparoscopic approach has had significant advances in recent years mainly because of greater surgeon training (**Figure 1**). This results in better use of the approach. The evidence in the world literature reports better results, such as postoperative ICU stay, mortality, reinterventions, and complications such as pancreatic and enterocutaneous fistula. In our study, laparoscopic management presented 0% mortality with a mean follow-up of 1 year. Similar results are reported in the literature, which are reported for minimally invasive approaches of 9%^(1,3,9,10) compared to open management, where we

observed a rate of 48% (results comparable to those documented in the literature of 45%–50%)^(4,9,11).

In terms of postoperative organ failure, laparoscopic management in the population decreased by about 40% from day 1 to day 2 and 20% from day 2 to day 3. These results are not evidenced in any study evaluated in the bibliography. However, in a series of cases, postoperative *de novo* organ failure was evaluated and decreased by about 25% in patients with minimally invasive approaches⁽³⁾.

Additionally, we observed that procalcitonin (PCT) was used as an infection marker in most of our patients (73%) prior to imaging studies. We established a 1.8 ng/mL cutoff point (taken from previous studies)^(5,6,8,12) and, given recent advances with PCT as a useful biomarker for antibiotic initiation in pancreatitis, we wanted to observe its behavior compared to the *computed tomography severity index* (CTSI) and mortality. PCT > 1.8 ng/mL was found to be related to a higher CTSI. In terms of mortality, we found that a PCT < 1.8 ng/mL was associated with lower mortality rates (out of 12 patients with PCT < 1.8 ng/mL, 11 had no mortality). This could reflect a possible relationship between procalcitonin elevation and pancreatic inflammatory status.

In microbiological terms, patients had a polymicrobial behavior with a predisposition to enterobacteriae colonization, which is related to what is reported in the literature^(7,13,14). Regarding antibiotics, there is a tendency to use carbapenems (more precisely meropenem) as described in international guides and recent studies. These studies indicate that their use, or that of ertapenem, has favorable results to control these infections^(5,7,8,14-41).

Given the above, as observed in our results, and considering what has been reported in the world literature, the minimally invasive laparoscopic approach shows promising results as it reduces, in considerable terms, the morbidity and mortality of our patients and hospital costs due to a decrease in general hospital stay and ICU. However, these results depend on multiple additional factors, such as the patient's age, comorbidities, and the surgeon's training, which is not assessable in the present study due to its observational nature.

The observed behavior of procalcitonin is promising. Recently, studies in the UK, such as PROCAP, sought to establish a relationship between PCT and the initiation of antibiotic therapy in pancreatitis^(7,17-25,42-45). Although no study adequately reveals a predictive capacity of procalcitonin in this pathology^(5,7,8,16,26-41), we can evidence a trend of this marker as a predictor of mortality in our study. However, more prospective studies are needed to confirm this hypothesis.

LIMITATIONS OF THE STUDY

The observational and retrospective nature prevents the hypotheses formulation with statistical power. However, based on the observational behavior of the results, it invites to generate hypotheses to be used in prospective studies that confirm what has been evaluated in this series of cases.

CONCLUSIONS

Currently, infected pancreatic necrosis is still a difficult pathology to manage surgically and a challenge for the surgeon. Stepwise and minimally invasive management should be of choice, always trying to avoid a surgical procedure that, if necessary, should be addressed laparoscopically since it presents better results in terms of mortality, morbidity, and general hospital and ICU stay. Procalcitonin could be a useful biomarker for predicting complications or mortality in these patients. However, more prospective studies are needed.

Conflicts of interest

None of the authors claims to have conflicts of interest.

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Rectal Cancer: Management Trends and Changes. Concepts for Gastroenterologists and Surgeons

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Abstract

Rectal cancer is the third most frequent cancer in Colombia and constitutes a diagnostic and therapeutic challenge for gastroenterologists, surgeons, and oncologists. Diagnostic evaluation and the study of its locoregional and systemic extension have been modified by new imaging methods, enabling an accurate view of anatomical structures that could not be easily examined before. The availability of these new tools in disease staging has significantly impacted therapeutic decisions and the choice of a specific treatment path for each patient, rationalizing the use of neoadjuvant therapies and the performance of surgery with correct anatomical criteria. The preceding has been essential to achieving the best outcomes with the least associated postoperative morbidity. This article will review and explain in detail the most recent changes and up-to-date recommendations for managing rectal cancer.

Keywords

Rectum, neoplasms of the rectum, proctectomy, staging of neoplasms, chemotherapy, radiotherapy.

INTRODUCTION

Colorectal cancer is the third most common type of cancer in Colombia. Nineteen thousand two hundred fifty-eight new cases were diagnosed in 2018. Only 13% of them corresponded to stage I, while 40% were in stages III or IV. 26% of the cases did not have a correct staging⁽¹⁾. The opportunity for diagnosis and management has improved, but there are still many patients without adequate oncology treatment. Rectal cancer is a complex disease. Its own natural history and difficult anatomical location make imaging

evaluation less accurate, and the surgical dissection is more demanding. These attributes produce substaging, inappropriate neoadjuvant and adjuvant treatments, and surgeries with resection margins that, if positive, will decrease the probability of healing and long-term survival with an adequate quality of life.

This is why it is pertinent to review the recent changes in evaluation images, staging, surgical technique, and complementary treatments. Those that provide better results for the patient will be chosen and implemented in clinical practice routinely.

CHANGES IN ONCOLOGY NOMENCLATURE

The new terminology emerges from the new tools in imaging studies and the new anatomical concepts. It must be standardized and managed by all the specialists involved in management⁽²⁾. Note especially the different staging possibilities according to the magnetic resonance imaging (MRI) during the preoperative. **Table 1** describes the current terms and their abbreviations used in this review.

Table 1. Oncology nomenclature

CRM: Circumferential resection margin
cTNM: Clinical staging according to AJCC
EMVI: Extramural vascular invasion
MRF: Mesorectal fascia
MSI: Microsatellite instability
mrTNM: MR staging
pTNM: Definitive pathological staging
CR: Complete response
LR: Local recurrence. Tumor reappearance within 5 years of pelvic follow-up
OS: Overall survival. Live patients after 5 years of follow-up
PFS: Progression-free survival
TME: Total mesorectal excision
TNT: Total neoadjuvant therapy
ypTNM: Post neoadjuvant definitive pathological staging
yTNM: Imaging staging after neoadjuvant therapy

AJCC: American Joint Committee on Cancer; MRI: Magnetic resonance imaging. Source: Table made by authors

CHANGES TO CLINICAL GUIDANCE GUIDELINES

Cancer reference guides have had changes in their updates. There are two main guides: The National Comprehensive Cancer Network (NCCN)⁽³⁾ and the European Society for Medical Oncology (ESMO)⁽⁴⁾. When comparing, there are fundamental differences in both. ESMO guidelines have had greater adherence in surgeons recently. However, most oncology groups follow the guidelines defined by NCCN.

Differences between recommendations in NCCN and ESMO guidelines

For years, in the NCCN guidelines (**Figure 1**), the preoperative study was based on rectal ultrasonography (2004–2012), defined by Sauer's study, where ultrasonog-

raphy was indicated in all patients⁽⁵⁾. In the 2017 update, MRI was suggested as the preferred study, and in May 2020 update, simple rectal MRI became the study of choice. Rectal ultrasonography is only for early selective cases. In this last update, CRM was considered a fundamental factor in decision-making to define surgical management, indication, and type of neoadjuvant, and as a determinant of different chemotherapy schemes⁽²⁾. Decision-making continues to be based on classic TNM, where un-subclassified T3, T4, and positive nodes are the primary indication for neoadjuvant chemoradiotherapy (CRT).

The European ESMO guidelines (**Figure 2**) changed the parameters of decision-making based on the Mercury⁽⁶⁾ studies. Primary tumor size (T) is subclassified according to anterior or posterior mesorectal fat penetration at T3a (< 1 mm), T3b (2-5 mm), T3c (> 5 mm), and T3d (> 15 mm). Positive or negative CRM determines decision making, i.e., nodal status is important but not paramount. Staging is based on the subclassification of T3 and the status of CRM^(6,7). According to these guidelines, patients with T1, T2, and T3a and b CRM (-) can be directly taken to surgery.

In the ESMO guidelines, neoadjuvant therapy is recommended in T3c, T3d, T4, and CRM positive or at commitment risk. A good surgical technique ensures the resection of all nodes under TME, which was defined and standardized by Heald in 1986. Positive nodes are not an absolute factor in making decisions before operating⁽⁸⁾. Positive nodal involvement is important in neoadjuvant decision-making if it is part of a positive CRM. If the patient has positive nodes in the MRI, but the MRF and CRM are free, this does not necessarily imply sending the patient to CRT. This is a fundamental difference in the ESMO guide.

The ESMO and NCCN guidelines consider organ preservation strategies, in which patients with tumors classified as cT2N0M0 or cT3a and b of the lower rectum may be included for neoadjuvant therapy. The ESMO guide recognizes the “wait and watch” (WW) protocol, reported in Brazil more than 14 years ago by Habr-Gama *et al*, not only as a protocol followed in experimental groups⁽⁸⁾ but as a reality to follow, where a complete clinical response is obtained in 37% to 50% of patients^(9,10).

CHANGES IN ANATOMICAL DIAGNOSIS

An anatomical diagnosis must be performed for rectum cancer. The diagnosis has been traditionally defined by the third portion, where the tumor is located. The rectum is divided into the upper, middle, and lower third. The lower third ranges from 0 to 5 cm, the middle from 5 to 10 cm, and the upper one from 10 to 15 cm from the anal ridge. It is important to describe if the tumor is felt by digital rectal exam and

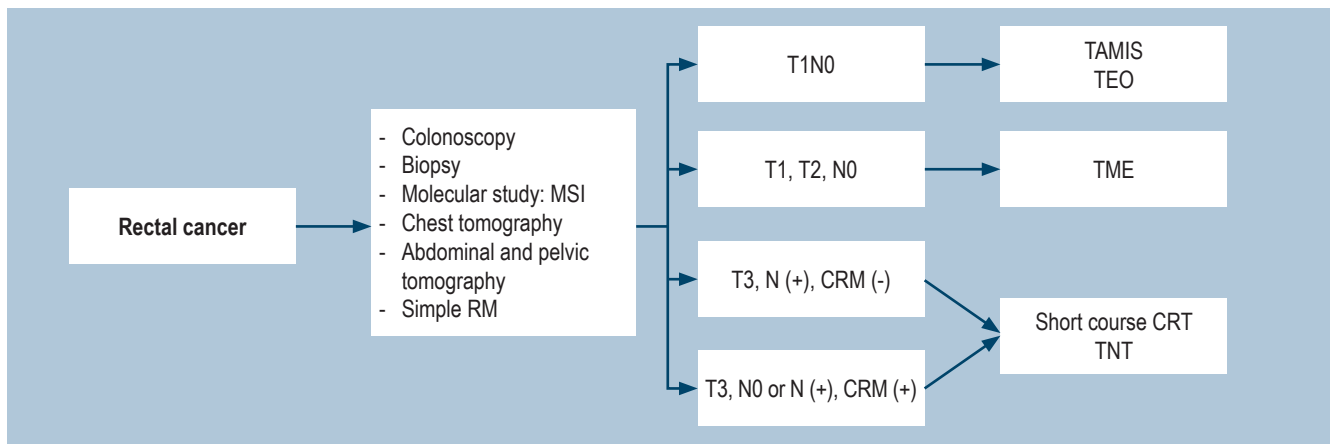


Figure 1. Recommendations for the management of rectal cancer according to NCCN guidelines. CRM: Circumferential resection margin; MSI: Microsatellite instability; N: Nodal state; CRT: Chemoradiotherapy; MRI: Magnetic resonance imaging; T: Primary tumor size, TAMIS: Transanal minimally invasive surgery; TEO: Transanal endoscopic operation; TME: Total mesorectal excision; TNT: Total neoadjuvant therapy. Taken from⁽³⁾.

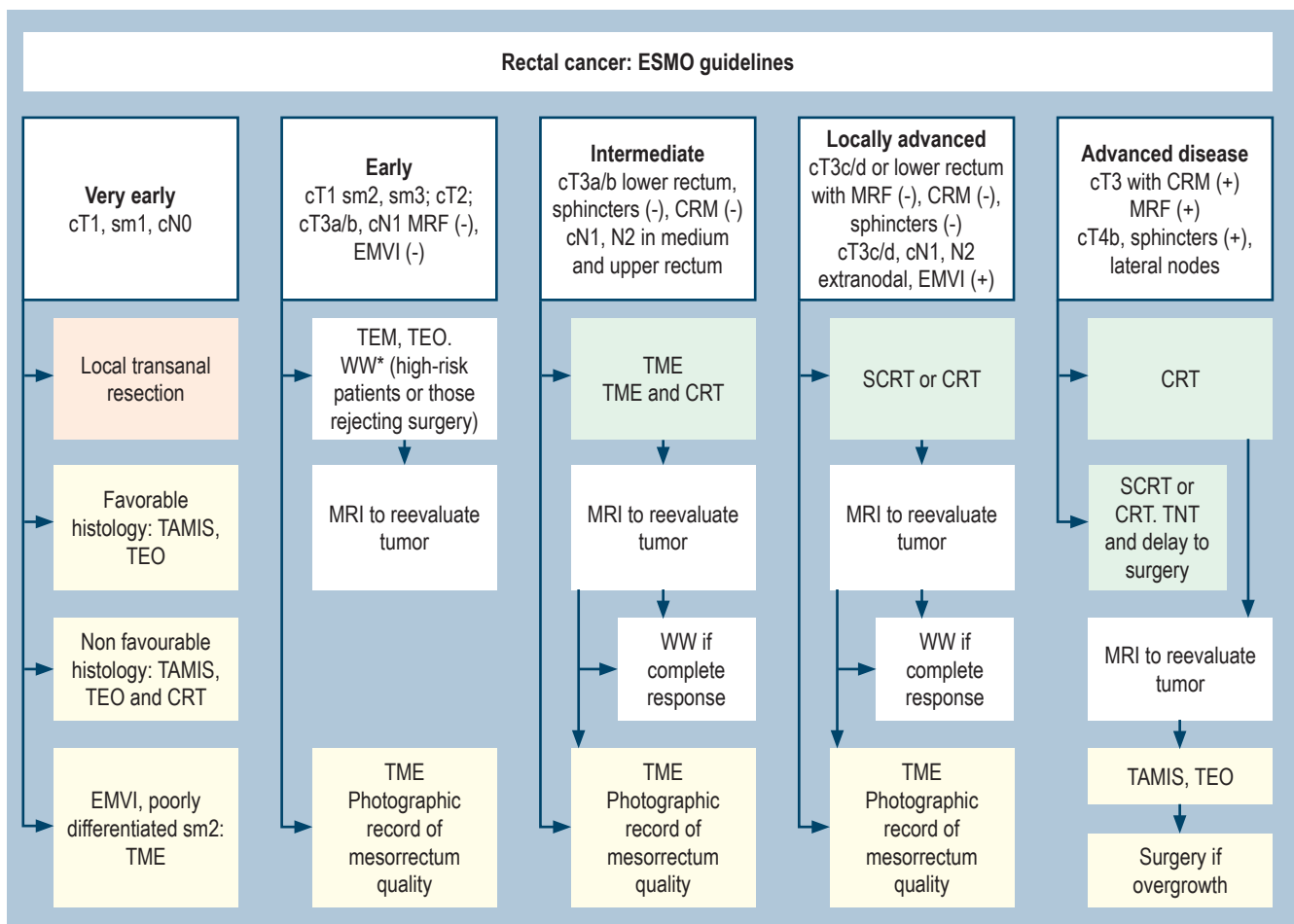


Figure 2. Recommendations for rectal cancer management according to ESMO. cN: Clinical nodal status; CRM: Circumferential resection margin; cT: Primary clinical tumor size; EMVI: Extramural vascular invasion; MRF: Mesorectal fascia; CRT: Chemoradiotherapy; MRI: magnetic resonance imaging; sm: submucosa; TAMIS: Transanal minimally invasive surgery; TEM: Transanal endoscopic microsurgery; TME: Total mesorectal excision; TEO: Transanal endoscopic operation; TNT: Total neoadjuvant therapy; WW: Watch and wait. Source: ESMO rectal cancer guidelines.

if it is fixed. Semiologically, the distance in centimeters may vary when the colonoscope, which is flexible, is taken as a measuring instrument. The use of rigid rectosigmoidoscopy to measure this distance has been described, but this is a recommendation with little adherence. It is advisable, as a tool, not only to define the tumor height in centimeters and its relationship with the Houston's rectal valves during colonoscopy. Also, it is recommended to establish the location of the peritoneal reflection using MRI. It simply defines whether the tumor is intraperitoneal or extraperitoneal and whether the peritoneal reflection is compromised.

The lower third will comprise the extraperitoneal rectum, where the CRM is evaluated. The anterior face in the middle third is intraperitoneal, and its lateral and posterior faces are extraperitoneal. The MRF will be evaluated in this area, while the upper third is intraperitoneal. The distance from the anal ridge to the tumor in centimeters, the location and fixation of the tumor by a digital rectal exam, the colonoscopic description, and the MRI with the peritoneal reflection assessment will determine the anatomical diagnosis (**Figure 3**)⁽¹¹⁾. However, tumors in the middle third could have an intraperitoneal and extraperitoneal component. This particular aspect will be definitive to determine the neoadjuvant decision and the surgical technique to be performed: a total or partial excision of the mesorectum.

CHANGES IN PHARMACOLOGICAL MANAGEMENT BY THE ONCOLOGIST

Management is determined by the degree of tumor tissue invasion (T3, T4), the number of nodes, and negative sec-

tion edges. Finding more than 12 nodes was the quality measure for surgery in rectal cancer. Less than 12 nodes were considered an incomplete surgery, a candidate for adjuvant therapy. Currently, the oncologist must analyze the same factors as the radiologist, the surgeon, and the pathologist (the CRM, the TME quality, and the presence of EMVI). From the point of view of LR and OS, these additional factors are the ones that have the most impact. The most interesting thing is that they can be evaluated with a simple MRI without contrast from the beginning of the patient's study, in the follow-up MRI after neoadjuvant surgery, and confirmed in the definitive pathology⁽¹²⁾.

The positive resection margin, or rectal circumferential (both definitions are valid), is the presence of tumor, node, or EMVI less than 1 mm from the circumferential margin in the extraperitoneal lower rectum. That edge is determined when reviewing the MRF in the MRI or the Indian ink in the pathology. If the measurement is in the upper rectum, it will correspond to MRF. If the measurement is in the extraperitoneal rectum, it will correspond to CRM. Of these factors, the one with prognostic value and affects the LR and OS is the positive CRM given by tumors (**Figure 4**)^(13,14).

CHANGES IN STAGING IMAGES

Simple MRI with rectal protocol is the primary examination for staging and defining the subclassification of T, CRM, and the presence of EMVI. The inferior rectum provides other parameters, such as the tumor relation with the sphincter external mechanism and the intersphincteric groove. Properly reporting the CRM involves the perfect description of the

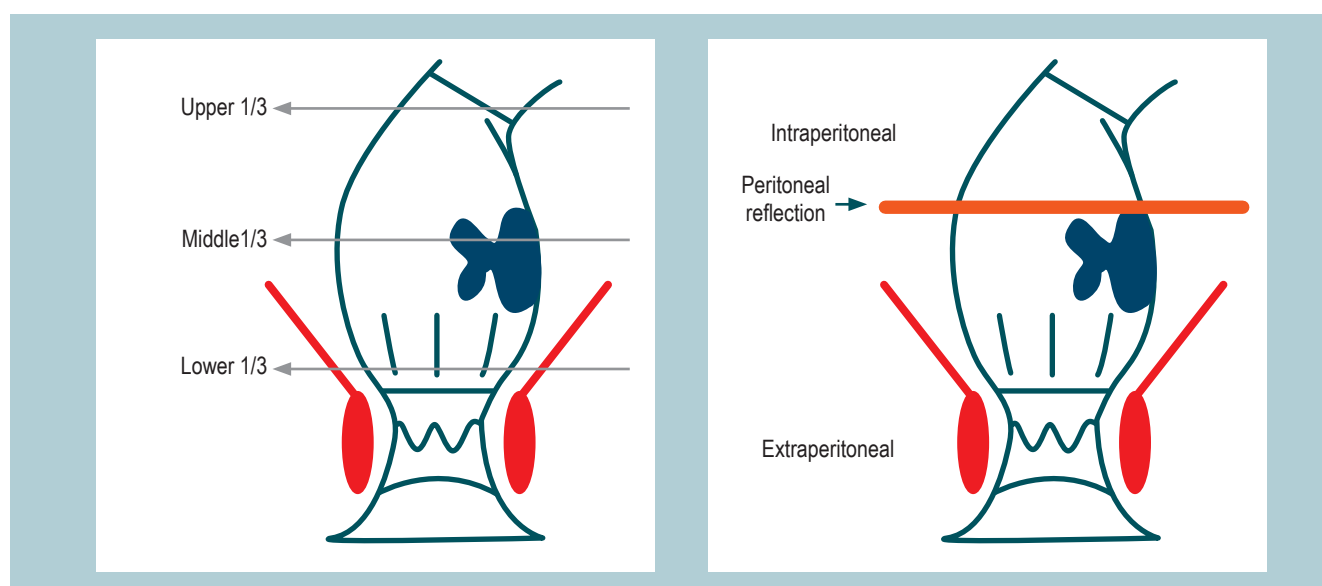


Figure 3. Anatomical diagnosis in rectal cancer. Source: Authors' file.

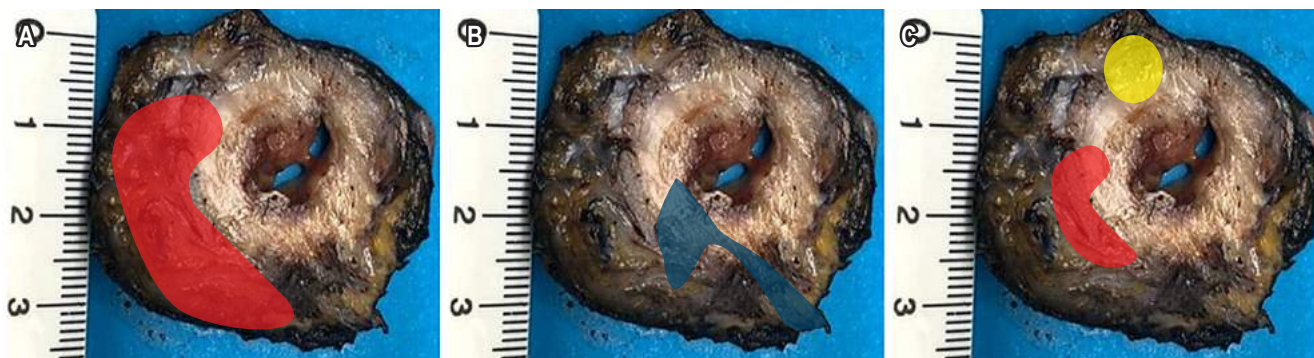


Figure 4. **A.** Tumor-positive CRM (red). **B.** EMVI positive CRM (blue). **C.** Node positive (yellow) CRM. Source of images: Authors' file.

MRF. Recognizing it in the images ultimately helps establish an adequate staging, make the oncological management decisions, and plan the surgical technique.

If the neoadjuvant decision was made by positive CRM or by the risk of being positive, restaging is done with an additional simple MRI, evaluation of T2 sequences, restriction to diffusion, and tumor regression index. This evaluation will be done depending on the type of neoadjuvant therapy performed, if conventional, 6 weeks after the radiotherapy is finished. If it were TNT (a new concept), the measurement would be made at the end of the consolidation chemotherapy. One of the frequently found difficulties in the study is that it is usually requested as a pelvic MRI. If the MRI with rectum protocol is not specified and requested, the technician will make the alignment and reconstruction of the images in an inadequate way. These images will not

be perpendicular to the rectum and the tumor axis, and it will not be possible to evaluate the subclassification of the T correctly. It is advisable to establish, with their working group, the revision of the image reconstruction technique (**Figure 5**)^(14,15).

CHANGES RELATED TO THE INDICATION OF SURGERY AS INITIAL TREATMENT

Patients with preoperative staging reporting T1N0M0 would be candidates for TME or transanal minimally invasive surgery by any of the existing platforms: transanal minimally invasive surgery (TAMIS), transanal endoscopic operation (TEO), or transanal endoscopic microsurgery (TEM).

Lower third T2N0M0 patients may be taken to initial surgery or be candidates for an organ preservation protocol.

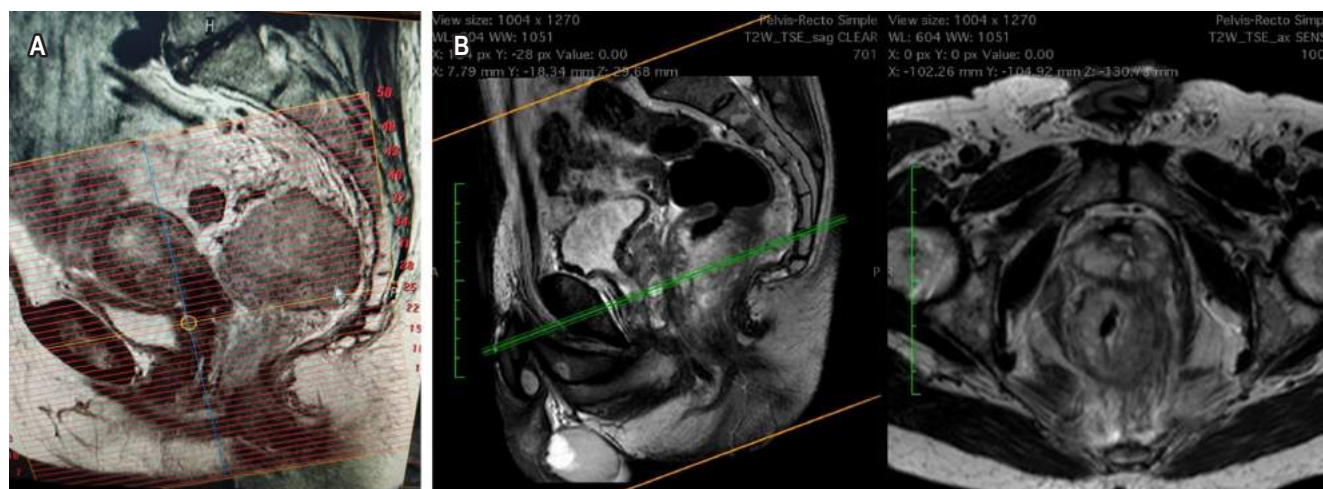


Figure 5. **A.** Simple rectum MRI. Planning of the cutting axis of the reconstruction packages for an actual staging of T. **B.** Verification that the axial cut corresponds to a perpendicular reconstruction to the tumor axis. Source of images: Authors' file.

This decision should arise at a multidisciplinary board as part of a neoadjuvant CRT plus consolidation chemotherapy program (this is the WW protocol). All patients with upper third cancer are candidates for immediate surgery, as long as the MRI does not describe peritoneal reflection involvement or risk of MRF involvement. Likewise, patients with lower, middle, or upper third cancer classified as T2 or T3a/b, negative CRM, with intact MRF, and whom the surgeon believes is feasible to perform a TME or partial resection of the mesorectum with 5 cm of distal margin, can go to surgery directly.

Neoadjuvant treatment is reserved for T3c/d and T4 patients, those with tumors with positive CRM or at involvement risk of the circumferential margin and with extension to the intersphincteric groove, as well as patients with selected N1, N2, or lateral nodes. This has represented a fundamental change in the management algorithm. The nodal status is not necessarily what determines the need for neoadjuvant therapy. According to the ESMO guidelines, the presence of positive nodes in the middle or upper third, with free MRF, can be taken to surgery. This is a big difference from the NCCN guidelines' recommendations, which send patients to chemotherapy and radiotherapy first. Patients with lower rectal cancer, where their surgery may involve performing an abdominoperineal resection (ARP), or an intersphincteric coloanal resection, may be treated with an organ preservation strategy from T2N0 onwards. New radiation schemes and consolidation chemotherapy may generate a higher percentage of complete or near-complete clinical responses with this strategy.

Neoadjuvant therapy allows a complete clinical response in the organ preservation strategy, which is the basis of WW. However, in certain cases, it could give an almost complete response or a decrease in staging in T, a scenario that can be managed with local resection, a TAMIS or TEO approach, and that should only be performed by expert groups in the management of rectal cancer^(16,17). This last approach in the almost complete response after neoadjuvant therapy is still under discussion.

The complete clinical response we observed in our setting is between 11% and 20% when using standard CRT. The schemes used in Brazil are extended CRT with 5400 centigray (cGY) and consolidation chemotherapy based on 5-fluoracil or oral capecitabine⁽¹⁸⁾. This scheme is indicated in patients with preoperative staging from T2N0M0 onwards, who obtain a 50% CR. Complete clinical response after TNT has been reported in 50%–65% of patients in certain studies, such as the OPRA⁽¹⁹⁾ study. These results were not seen with previous algorithms. Other reports indicate an overall rate of 37% CR when patients with early and locally advanced stages are included.

CHANGES IN THE NEOADJUVANT THERAPY

Neoadjuvant therapy is indicated in patients with upper third rectal cancer with peritoneal reflection involvement, patients with T3c/d middle and lower third rectal cancer, positive T4, CRM, and EMVI, and in organ preservation strategy in the lower rectum in patients \geq T2N0M0⁽²⁰⁾.

There are several definitions that should be clarified in chemotherapy. As part of standard CRT, chemotherapy is called 5-fluoracil or capecitabine-based sensitization chemotherapy. If a complete scheme is applied before radiotherapy, it is called induction chemotherapy. If it is applied concomitantly or after standard CRT, it is called consolidation chemotherapy. Consolidation chemotherapy with 5-fluoracil or capecitabine is used in the WW protocol. The 16-week oxaliplatin addition scheme is usually applied when staging includes positive n and CRM, or T4 additionally. TNT groups together all the schemes where systemic chemotherapy, which used to be given after surgery, is now given before surgery.

Radiotherapy schemes may be a short course, where the patient receives 500 cGY for 5 days, for a total of 2500 cGY. Waiting 4 to 6 weeks produces the same biological effect as the conventional long scheme, as long as 6 to 8 weeks are taken to wait to perform the surgery. If used as part of TNT, the patient receives consolidation therapy 15 days after the end of the short cycle. The long standard radiotherapy scheme is 5040 cGY in 25 sessions of 200 cGY per day, applied in 6 weeks. The Brazilian scheme applies 5400 cGY, corresponding to 4500 cGY of external radiotherapy and an additional reinforcement (boost) of 900 cGY focused on the tumor. In practical terms, it is 2 more days of radiotherapy, followed by consolidation chemotherapy (Figure 6)⁽¹⁸⁾.

CHANGES AT THE TIME OF OPERATING

T1 tumors are treated with TME or local transanal resection. T2, T3a/b lesions of the middle and lower third should go to surgery only if a TME is feasible. If the lesion is in the lower rectum, and an organ preservation scheme is considered, extended CRT plus consolidation is given. At the end of chemotherapy, it is re-evaluated, and, based on the results, the decision to operate or to observe if a complete clinical response was obtained is made. If the answer is almost complete (a new concept to be discussed), the observation can be extended to 6 weeks to achieve a CR and make an organ salvage⁽²¹⁾.

Combining the classics and new concepts for a T3c/d, middle and lower third T4, we have the following alternatives:

- Traditional scheme: Long-course CRT. Wait for 6 weeks and re-evaluate with MRI. The surgery is per-

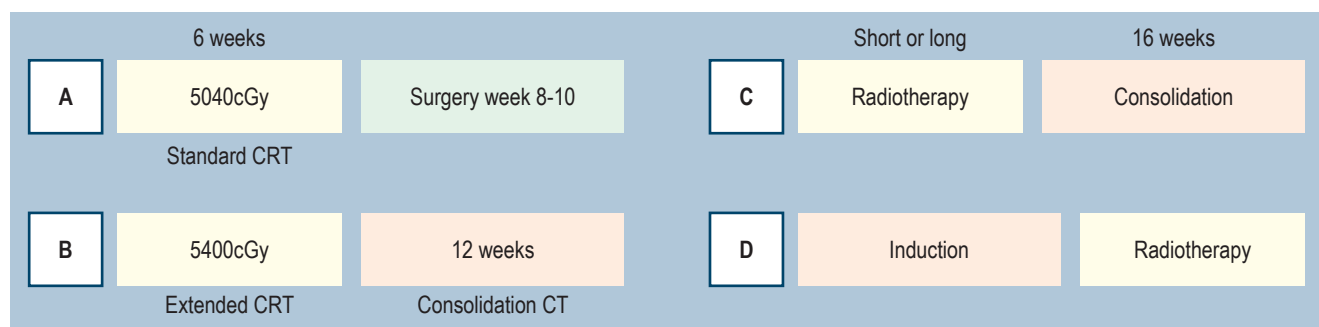


Figure 6. **A.** Standard CRT. **B.** Extended CRT, Brazil. **C.** TNT, Consolidation chemotherapy. **D.** TNT, Induction chemotherapy. CT: chemotherapy; CRT: chemoradiotherapy. Source: Scheme made by authors.

formed between weeks 8 to 12. After this, it is decided if there is adjuvant chemotherapy. This is the most used scheme of neoadjuvant therapy, surgery, and adjuvant care, which we are already abandoning.

- Before a tumor with a high risk of sphincter loss, it is possible to choose a TNT scheme with 4-month consolidation chemotherapy, re-evaluation with MRI, and surgery performed at 6 months. The TNT schedule can be performed with short or long scheme radiotherapy and induction or consolidation chemotherapy. In the case of CR, the WW protocol can be applied to save the rectum. If the response is almost complete, you can opt for a TME or a minimally invasive transanal approach to achieve the preservation goal.

Some studies support each of these options and others are in progress to define the best strategy with impact on LR and OS (RAPIDO and OPRA studies). Preliminary

reports give complete clinical responses between 50% and 64% of cases^(22,23).

WHAT CHANGED IN THE SURGERY?

Surgery is no longer defined in terms of anterior resection, low anterior resection, or ultra-low anterior resection. Currently, it is described in terms of TME for lower third tumors, some middle-third tumors with extraperitoneal involvement, and specific mesorectal excision or partial mesorectal excision (pME) for upper or middle third (intra-peritoneal) tumors. In these cases, the distal margin should be 5 cm. The concept of 2 cm of margin in the non-irradiated rectum, or 1 cm of distal margin in irradiated recta, refers to the mucosal section margin for patients undergoing TME (**Figure 7**)⁽²⁴⁾. TME can be performed by open, laparoscopic, or robotic surgery, depending on the surgeon's expertise.

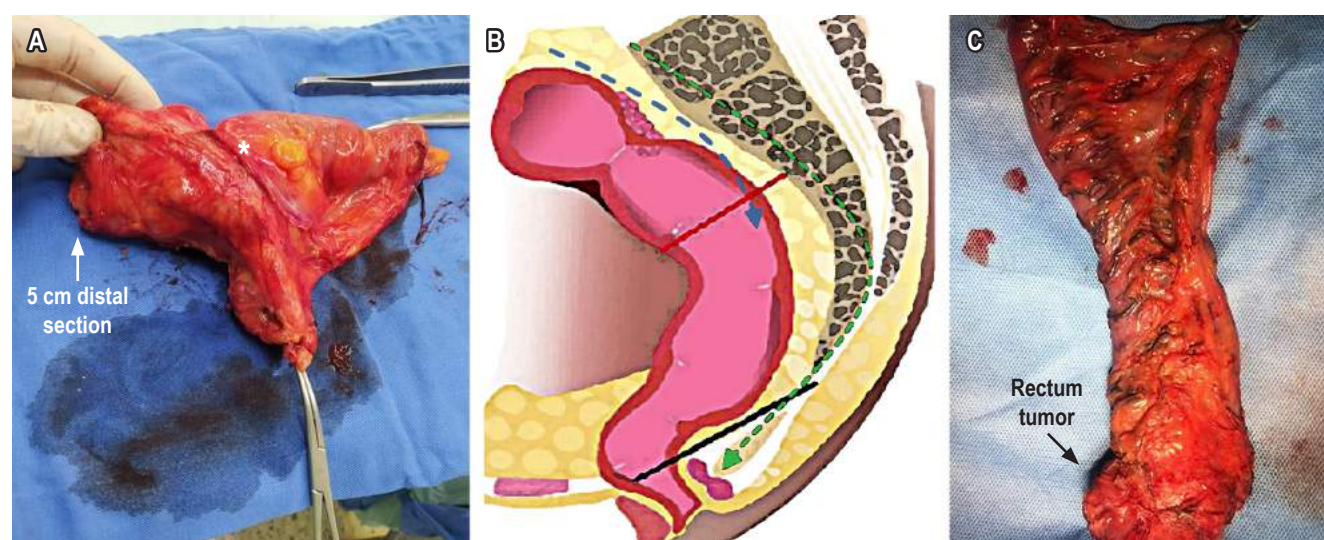


Figure 7. **A.** Specific partial or mesorectal excision (*tumor location). **B.** Mesorectal excision scheme. TME: green dotted lines to levator ani plane (black line). pME specific: blue dotted lines to distal section edge (red line). **C.** TME. Source: Authors' file.

How is TME defined?

The rectum's meso must be completely resected in the TME until the levator ani, through Waldeyer and Denonvillier's embryological fusion fascia. The surgeon and pathologist should evaluate the quality of this resection. The histopathologic report should describe whether the resection known as the mesocolic plane is complete, incomplete, or intramuscular. This characteristic has been defined as a prognostic factor of recurrence and OS.

In the last decade, a mesorectum approaching technique has been described in two ways: abdominal and perineal simultaneously. The direct transanal and transabdominal approaches are known as TATA. If the transanal approach is made with a laparoscopic perianal platform or device, the mesorectal dissection of the lower third is performed meeting the abdominal surgeon, the technique is known as transanal total mesorectal excision (TaTME)⁽²⁵⁾. It is a developing surgical option for obese male patients, where performing TME up to the levator ani is not easy. Additionally, this technique ensures the distal section edge⁽²⁶⁾. It has defenders and detractors, and still, its oncological outcomes are under discussion^(15,27).

Assessment of the presence of side adenopathies is a different concept in development and detectable only by MRI. These external nodes to the iliac vessels are currently considered a locoregional disease. They are not part of the conventional emptying of a TME. They are of special interest because, if they are detected by MRI and persist enlarged after radiotherapy, they have the indication of new surgery, known as pelvic lymph node dissection (PNLD).

Lateral nodes are responsible for pelvic recurrence if this surgery is not carried out⁽²⁸⁾.

WHAT CHANGED IN THE PATHOLOGY?

The processing of the surgical specimen in macro is as important as the findings of the microscopic study. Surgeons tend to open the surgical specimen to check the safe section edges. However, this technically makes it difficult for the pathologist to evaluate the CRM. The ideal scenario is to preserve the piece in the tumor area and partially open it so that the formaldehyde enters and the edges can be processed correctly. This allows measuring the distance in millimeters from the T, the CRM, the distance to the MRF, the extramural venous invasion, and the quality of the mesorectum. All this, in addition to the nodes, their number, the degree of tumor differentiation, the tumor size, and the histological subtype. The pathology report should include, in detail, the previously described information (Figure 8)⁽²⁹⁾.

CHANGE IN MOLECULAR BIOLOGY

Knowing tumor biology helps determine prognosis and treatment. There are two ways to study mutations: on the piece and biopsies or blood, known as liquid biopsies. IMS instability is determined in the biopsy and the piece. The mutation in MSH, MLH, and PMS2 is measured as well as the status of the KRAS: mutated or native.

These important factors in the prognosis direct the oncologist on whether to use chemotherapeutics. IMS is



Figure 8. Processing of the piece. **A.** Opening of the piece in the area without tumor. **B.** Ink marking of CRM and mesorectal fascia. **C.** Cut in donuts to evaluate the CRM. Source of images: Authors' file.

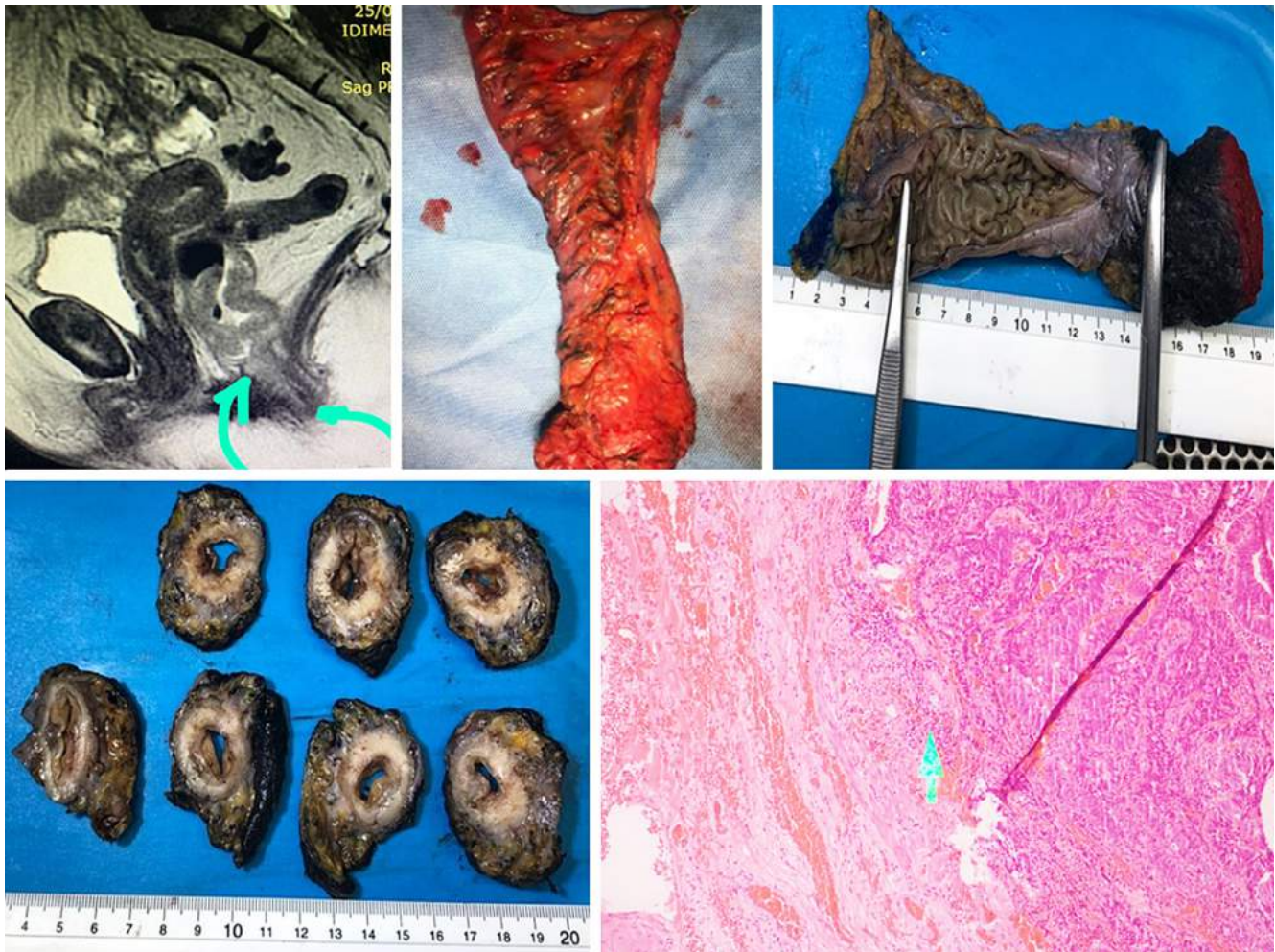


Figure 9. Multidisciplinary board (radiologist, oncologist, surgeon, gastroenterologist, radiotherapist, pathologist). Source of images: Authors' file.

associated with a poor response to fluoropyrimidines but with a better prognosis. Its presence supports the use of immunotherapy. The *ras* profile allows us to know whether biologics, such as epidermal growth factor (EGFR) inhibitors, should be used. In blood, the measurement of new carcinogenesis pathways (such as BRAF) will give treatment guidelines. Molecular staging is already a standard in studying rectal cancer patients⁽³⁰⁾.

CHANGE IN DECISION-MAKING: MULTIDISCIPLINARY BOARD

Ideally, decisions are made by an interdisciplinary team⁽¹⁾, which should be composed of gastroenterology, colorectal or gastrointestinal surgery, radiology, oncology, radiotherapy, and pathology. The existence of this board will help define, from the beginning, the management and route for each patient (**Figure 9**).

CONCLUSIONS

Recent evidence makes the diagnosis, locoregional and systemic staging, and treatment of rectal cancer known by all specialties involved in its management. The different public and private institutions must make efforts, research, and clinical groups to implement the diagnostic and therapeutic approach strategies presented here. The exposed changes are in **Figure 10**.

Conflicts of interest

The authors claim not to have conflicts of interest.

Source of funding

The present work was self-financed.

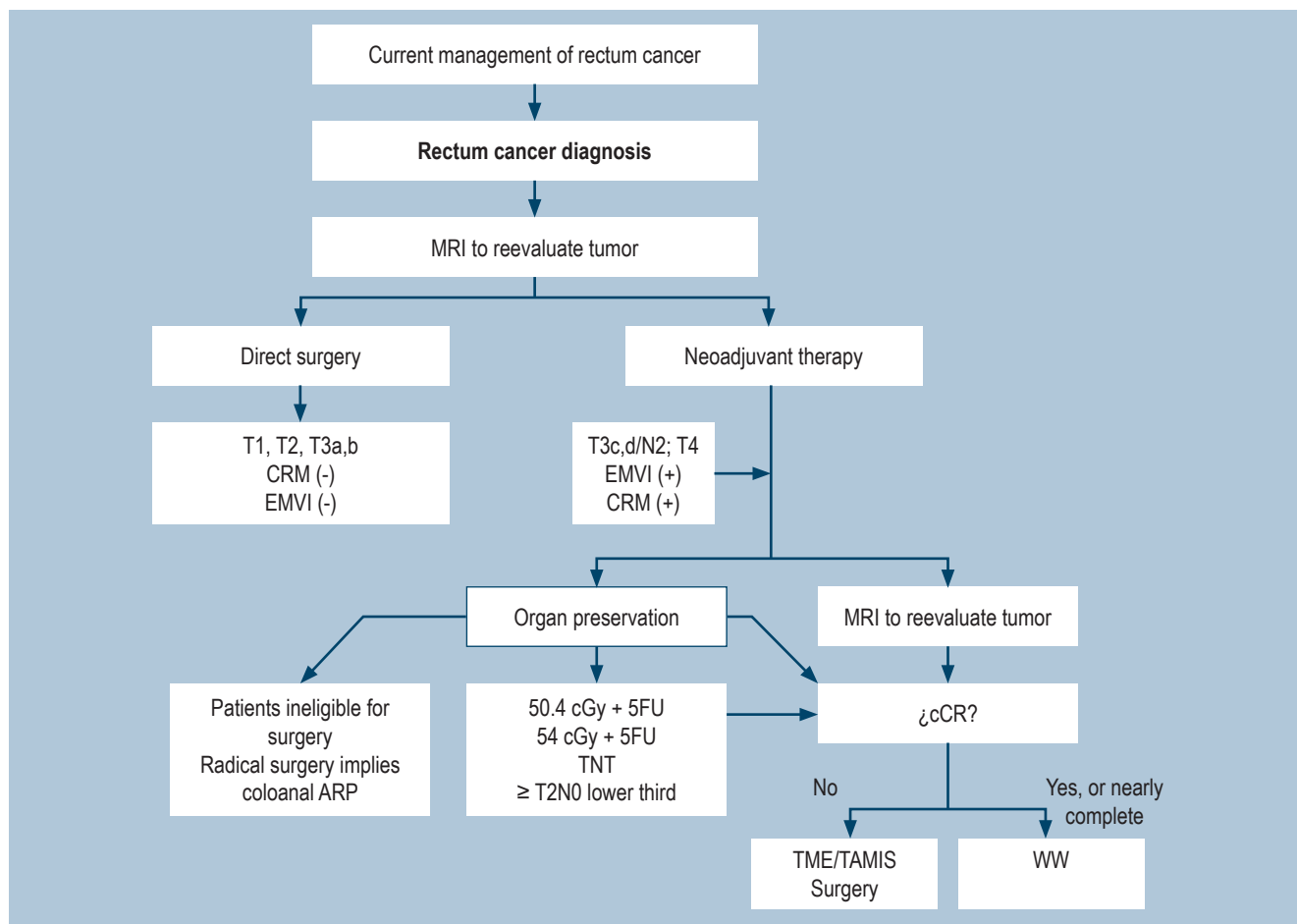


Figure 10. Flowchart for the current management of rectal cancer. 5FU: 5-fluoracil; cCR, complete clinical response; cGy: centigray; CRM: circumferential resection margin; EMVI, extramural vascular invasion; MRI, magnetic resonance imaging; TAMIS: transanal minimally invasive surgery; TME: total mesorectal excision; TNT: total neoadjuvant therapy; WW: Watch and wait. Source: Diagram made by authors.

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Esophageal Intramural Pseudodiverticulosis

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Abstract

A report of two cases of esophageal intramural pseudodiverticulosis, a very unusual disease, with other 240 cases reported in the entire world literature since 1960. Its etiology and pathogenesis are still not fully understood. However, it is believed that hypertrophy of the submucosal glands, with chronic inflammation, fibrosis, and consequent esophageal stenosis, causes dysphagia, which is the primary manifestation of esophageal intramural pseudodiverticulosis. The main diagnostic methods include the radiological examination of the esophagus with barium contrast (esophagogram) and esophagogastroduodenoscopy (EGD). Both reported cases were treated with endoscopic dilation, exemplifying the safety and efficacy of this therapeutic option for treating dysphagia in these individuals.

Keywords

Esophageal intramural pseudodiverticulosis, endoscopic dilation, dysphagia.

INTRODUCTION

Esophageal intramural pseudodiverticulosis (EIPD) is an extremely rare disease, first described in 1960 by Mendl *et al.* Since then, around 240 published cases have been collected worldwide until 2014⁽¹⁾. EIPD primarily affects men in their 60s⁽²⁾.

Its etiology and pathogenesis are not yet fully known. The main hypothesis to explain EIPD results from a hypertrophy of the submucosal glands with cystic dilation of the excretory ducts. During the illness course, inflammation of the submucosal glands can cause fibrosis of the esophageal wall, with consecutive stricture of the lumen. Esophageal stenosis leads to dietary impacts, malnutrition, and dysphagia, which is present in up to 80% of patients⁽²⁻⁵⁾.

Diagnosis is established by upper gastrointestinal endoscopy (UGE) and a radiological examination of the esophagus with barium contrast (esophagogram). Histological examination is essential to differentiate between benign and malignant stenosis. During UGE, numerous ostia can be visualized, measuring between 2 and 4 mm with whitish collections on the outside of the esophageal wall and stenosis. The esophagogram shows an esophageal stricture and small areas of contrast accumulation, corresponding to the pseudodiverticula⁽²⁾.

Conventional treatment is based on relieving symptoms. Dysphagia is treated by endoscopic dilation with Savary-Gilliard tubes. When there is gastroesophageal reflux and moniliasis, specific medications are used for their treatment. Most EIPD cases have a good evolution with this therapeutic scheme⁽³⁾. Esophagectomy was rarely necessary⁽⁶⁾.

MATERIALS, METHODS, AND RESULTS

Case 1

A 73-year-old female, native and resident of Barretos, SP, Brazil. A smoker who uses 60 packs per year. She suffered from progressive intermittent dysphagia for 17 years. During this period, she made a soft diet. She even had food impact treated by endoscopy. She sought medical attention when she had dysphagia for liquids, but the EIPD diagnosis took 1 year. During this period, she lost 35 kg and underwent a surgical gastrostomy. After diagnosis, she consulted for dilation with Savary-Gilliard tubes. The treatment was initiated with a 5.0 mm tube. After the second session, the 11 mm diameter was reached. At this point, she started eating solids, and the gastrostomy tube was performed. The treatment with dilatations was extended for 6 months, for a total of 5 sessions. She also received fluconazole to treat esophageal moniliasis, present in all performed endoscopies. Omeprazole was also administered for esophagitis due to gastroesophageal reflux disease (GERD), aggravated by a hiatal hernia. The patient had an excellent response to treatment and has remained asymptomatic for 3 years (Table 1 and Figure 1).

Case 2

VJR is a 55 year old male, born in Valparaíso, SP, resident of Tucuruí, PA, Brazil. He suffered from dysphagia for 10 years. He ate only soft and liquid foods in this period. He had food impact 4 times and required endoscopic extrac-

Table 1. Clinical picture, endoscopic findings, and therapeutic response of reported cases

Personal data	Case 1	Case 2
Sex	Female	Male
Dysphagia time (years)	Yes (17 years)	Yes (10 years)
Impact	Yes	Yes
GERD esophagitis	Yes	Yes
Moniliasis	Yes	Yes
Smoker	Yes	Yes
Uses alcoholic beverages	No	Yes
Weight loss (kilos)	35	No
Weight gain after treatment	Yes	Yes
Esophageal stenosis	Yes	Yes
Treatment with esophageal dilation	Yes (up to 11 mm)	Yes (up to 12.8 mm)
Dysphagia return time	Asymptomatic 3 years ago	6 months

GERD: esophagitis due to gastroesophageal reflux disease. Source: Table prepared by the author

tion. When he sought medical help, he drank fluids for 3 months. He reported symptoms such as dysphagia, pyrosis, and moderate gastroesophageal reflux in chronic use of omeprazole. The patient claims to consume alcoholic

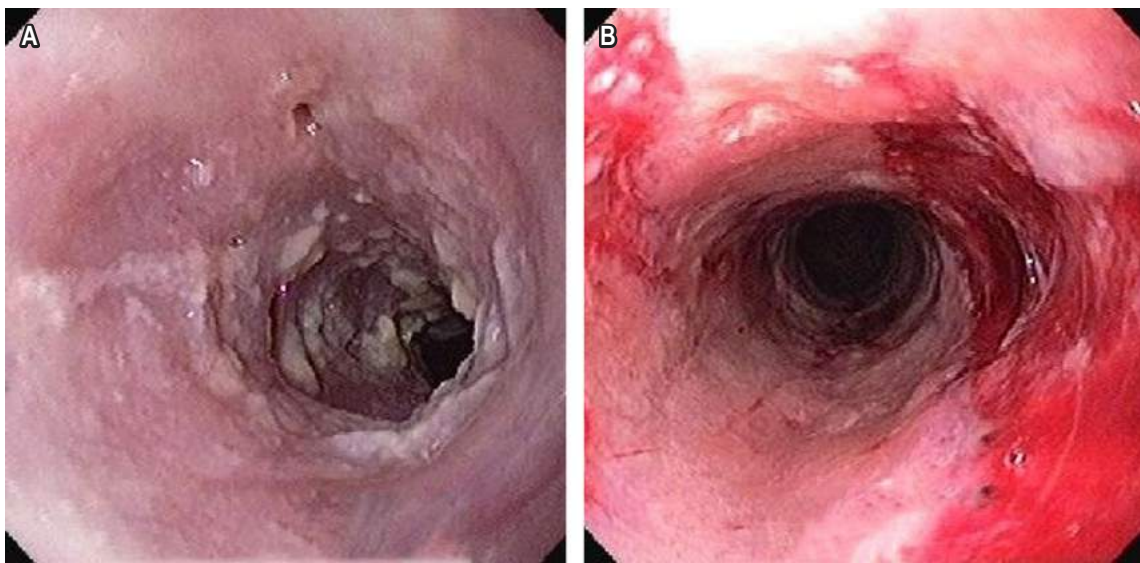


Figure 1. Endoscopic images of patient's EIPD from Case 1. **A.** Diagnostic image of EIPD for moniliasis. **B.** Image after endoscopic dilation. Source: personal file.

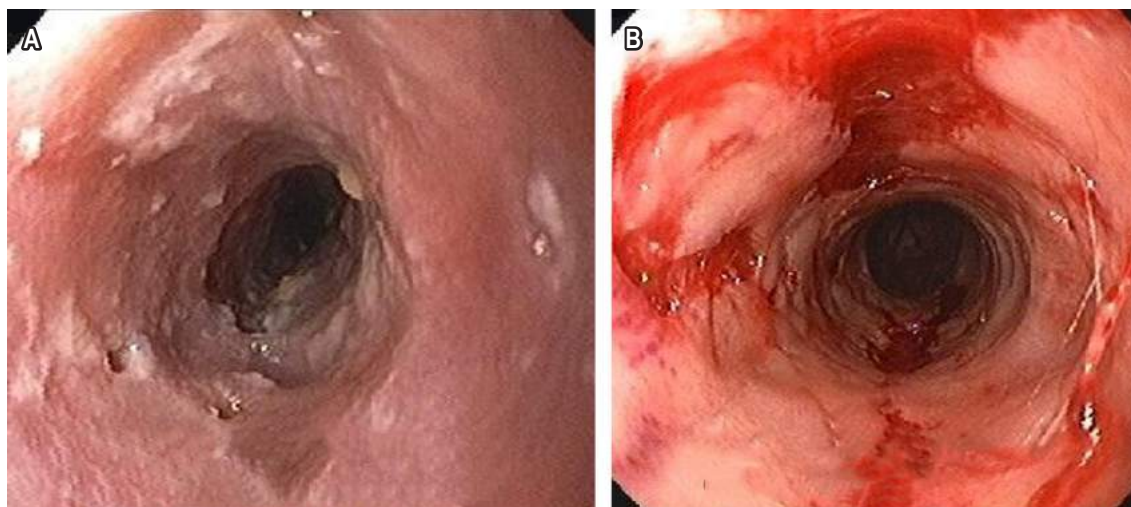


Figure 2. Endoscopic images of patient's EIDP from Case 2. **A.** Diagnostic image of EIPD for moniliasis. **B.** Image after endoscopic dilation. Source: personal file.

beverages at least once a month and is a smoker who uses 32 packs per year. EIDP was diagnosed 3 years ago through an upper gastrointestinal endoscopy when esophageal candidiasis was also found.

Initially, 3 sessions were held at 1-week intervals. Dilations began with 7.0 mm tubes. At the end of 3 weeks, they reached 12.8 mm with a complete reversal of dysphagia. Due to the distance between the state of Pará, where the patient resides, and the city of São José do Rio Preto, where he undergoes treatment, dilation sessions have been held every 6 months for the last 3 years. The patient reports remaining asymptomatic for 5 months until the dilation endoscopy presented dysphagia to solids in the last month. He also presents with moniliasis whenever digestive endoscopy is performed. From the beginning of the treatment, the patient gained 11 kilos (**Table 1** and **Figure 2**).

DISCUSSION

Dysphagia was the main symptom in the two cases reported in this study. It was also the main reason the individuals sought medical help. Similarly, more than 72% of patients in the following studies had dysphagia as their main symptom^(1-3,5-9).

Patients are over 70 years old in both reported cases, very similar to the data provided in most cases in the medical literature^(1-3,6,7,9-14). Except for patients with human immunodeficiency virus (HIV), who presented the condition at age 35 without evidence of moniliasis⁽⁸⁾, and at age 45 (**Table 2**)⁽⁵⁾.

Table 2. Summary of the main findings of the case reports in the medical literature

Datos personales	Número de casos	Porcentaje (%)
Years (average)	62 years	-
Woman	03	27.27
Man	08	72.72
Dysphagia	08	72.72
Impact	03	27.27
GERD esophagitis	07	63.63
Moniliasis	07	63.63
HIV	02	18.18
Smokes cigarettes	03	27.27
Uses alcoholic beverages	05	45.45
Esophageal stenosis	05	45.45
Treatment with esophageal dilation	07	63.63
No improvement after dilation	01	09.09
Dysphagia returned	00	00

GERD: gastroesophageal reflux esophagitis; HIV: human immunodeficiency virus. Source: Table prepared by the author.

In the total of the summarized studies in **Table 2**, a higher incidence of EIPD was demonstrated in men. However, in this report, one case was reported in a man and the other in a woman^(1,3,5,7-10,13).

Reflux esophagitis and fungal infection may accompany EIPD. In this study, both patients had GERD esophagitis and *C. albicans* infection. The authors^(2,6-10,12) reported cases of esophagitis due to GERD^(1-3,8,9,12,13), where a candid infection was found in the esophageal biopsy (**Table 2**).

Both patients in this study were treated with endoscopic esophageal dilation, medicines for esophagitis, and GERD moniliasis. Seven studies reported treatment with esophageal dilation and medication for existing pathologies in the literature^(1-3,5-7,9).

Case studies^(8,10,12,13) performed conservative treatment only with medication for existing pathologies. Only one of these cases⁽¹⁰⁾ showed no improvement in pseudodiverticula during the follow-up period (**Table 2**).

In this study's patients, improvement in dysphagia was felt after the first endoscopic dilation session. However, in case 2, there was a recurrence of dysphagia to solids 6 months after the last dilation session. This evolution is explained by the fact that this person lives 2200 km away from the healthcare facility where the treatment is performed, so he cannot carry out all consecutive dilations until a satisfactory esophageal diameter is established. The patient in case 1 received 5 consecutive sessions over 6 months and remains asymptomatic 3 years after the last endoscopic dilation session (**Table 2**).

CONCLUSION

Reports exemplify the difficulty of diagnosing EIPD and demonstrate that endoscopic dilation is a safe and effective option to treat dysphagia in these individuals.

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Endoluminal Vacuum Therapy (EVAC) in Managing Esophagogastric Anastomosis Fistula

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Abstract

Endoluminal vacuum therapy (EVAC) is a promising alternative for the endoscopic management of gastrointestinal fistulas or perforations that do not respond to endoscopic procedures using clips and stents or are even refractory to surgical procedures. In this case report, we describe the successful endoscopic closure of an esophagogastric anastomotic fistula using EVAC, connected to a vacuum system through a probe in the cavity, which did not close with clip management given the friability and edema of the peri-wound tissue. In conclusion, it is a successful alternative to treat these complications, which are sometimes difficult to resolve.

Keywords

Wound closure technique, endoscopy, esophageal fistula, surgical anastomosis.

INTRODUCTION

One of the most important complications after an esophagectomy is the anastomotic fistula, with an incidence between 1% and 30%⁽¹⁾. Among the alternatives of endoscopic management, we find the endoluminal vacuum therapy (Endo-Vac), a sponge connected to a nasogastric tube located in the defect to be corrected. It is connected to negative pressure⁽²⁾. This system decreases bacterial contamination and edema and stimulates tissue granulation through angiogenesis, gradually reducing the cavity size until closure is achieved^(3,4). Esophageal anastomotic fistulas are a life-threatening condition, between 0.8% to 11.6%, due

to the development of mediastinitis, pleural empyema, and sepsis^(5,6). Mortality rates of up to 18% have been found in cancer patients⁽⁷⁾. We present a case of esophagogastric anastomotic fistula managed with Endo-Vac.

CLINICAL CASE

A 69-year-old man with a history of gastric adenocarcinoma, extended to the gastroesophageal junction, staged III b (pT4N0M0), who has diabetes *mellitus*. The patient was taken to esophagogastric resection by laparoscopy and thoracoscopy with negative section edges, in management with adjuvant therapy and Capeox protocol. He presented oro-

pharyngeal dysphagia and odynophagia and a weight loss of 18 kg. On the 11th postoperative day, he showed signs of an inflammatory response with an esophagogram, which evidenced a fistula at the level of anastomosis. The endoscopic study found a 15 mm fistula in the anastomosis at 30 cm of the dental arches. Under the fluoroscopic vision, it presented extraluminalization outside the esophageal wall (**Figure 1**). Initial management consisted of placing 5 clips. Due to the mucosa friability, the total closure of the defect was not achieved.

Due to the persistence of a 5 mm fistula on the anastomosis, Endo-Vac therapy is performed with the GranuFoamTM sponge, connected to an intermittent drainage system with a negative pressure of 100 mm Hg (**Figure 2**). A laparoscopic jejunostomy was performed at the same time. Sponge replacement is performed at 7 days, and a reduction in the fistula defect is observed. At 2 weeks of therapy initiation, adequate wound healing is achieved without evidence of fistula. The sponge and nasogastric tube are removed with a 30 mm handle without complications. Endoscopic control one month and 3 months after the end of Endo-Vac therapy. Anastomosis with inflammatory changes and light decrease by 30%, caused by angulation effect and not by stenosis, allowing the equipment's easy passage (**Figure 3**). Management with proton-pump inhibitor was indicated, and dysphagia improved without chest pain.

DISCUSSION

This article describes a closure case of esophagogastric anastomotic fistula in a patient with a history of esophagogastric resection due to gastric adenocarcinoma, extended to the gastroesophageal junction. The closure was managed by placing endoscopic clips, with a partial closure of the fistula, and the Endo-Vac therapy by means of two replacements. An excellent result is obtained in managing this complex fistula without complications.

Although esophageal perforations are a rare clinical entity, they have a high mortality and morbidity rate. This represents a challenging paradigm in their management⁽⁸⁾. Treatment of anastomotic fistula depends on the cause, size, timing of the continuity solution, and the patient's nutritional status. The therapeutic plan includes support measures, antibiotic therapy, and, in some cases, antifungals, extraluminal collection drainage, and maintenance of enteral nutrition. Endoscopic management is less morbid than surgery⁽⁹⁾.

The treatment pillar of upper gastrointestinal fistulas is endoscopic therapy with clips or the OVESCO system for perforations less than 2 cm and endoscopic suture for perforations greater than 2 cm. The placement of self-expanding stents is reserved in cases where primary closure is not achieved⁽¹⁰⁾, with a greater success rate of 68.8%–90% in

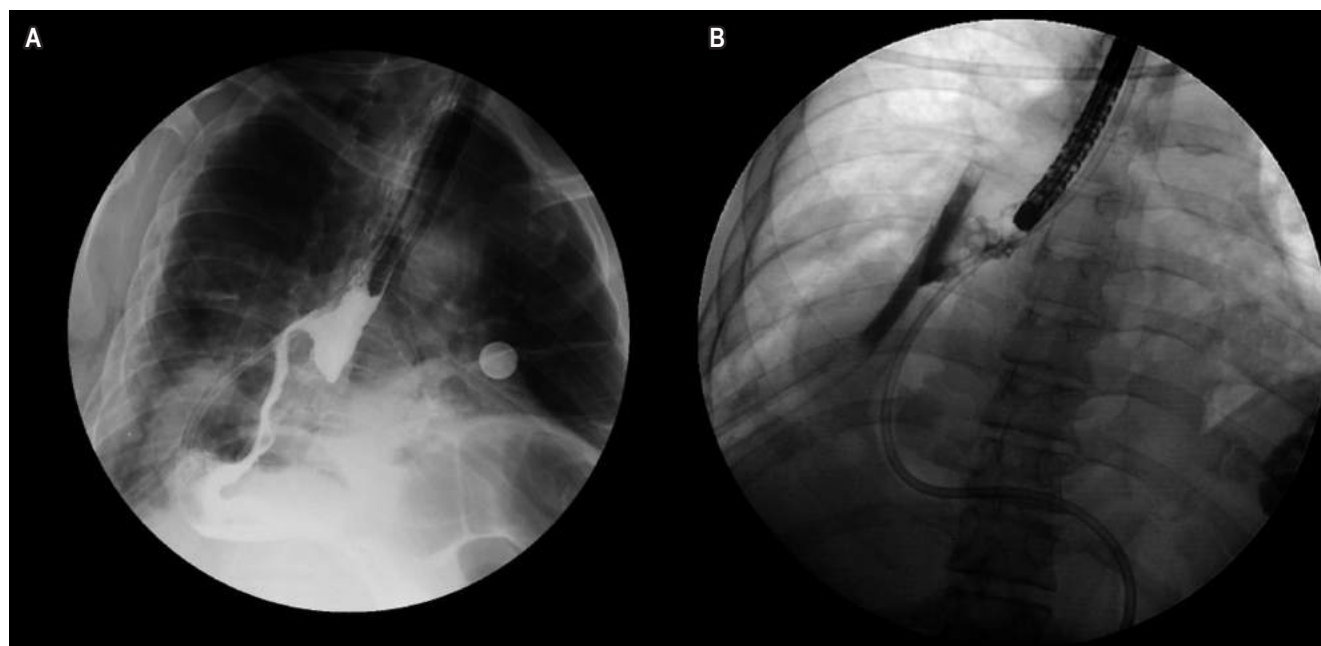


Figure 1. **A.** Esophagogram: fistula tract in the esophagogastric anastomosis. **B.** Irrigation of the contrast material with extraluminalization outside the esophageal wall.

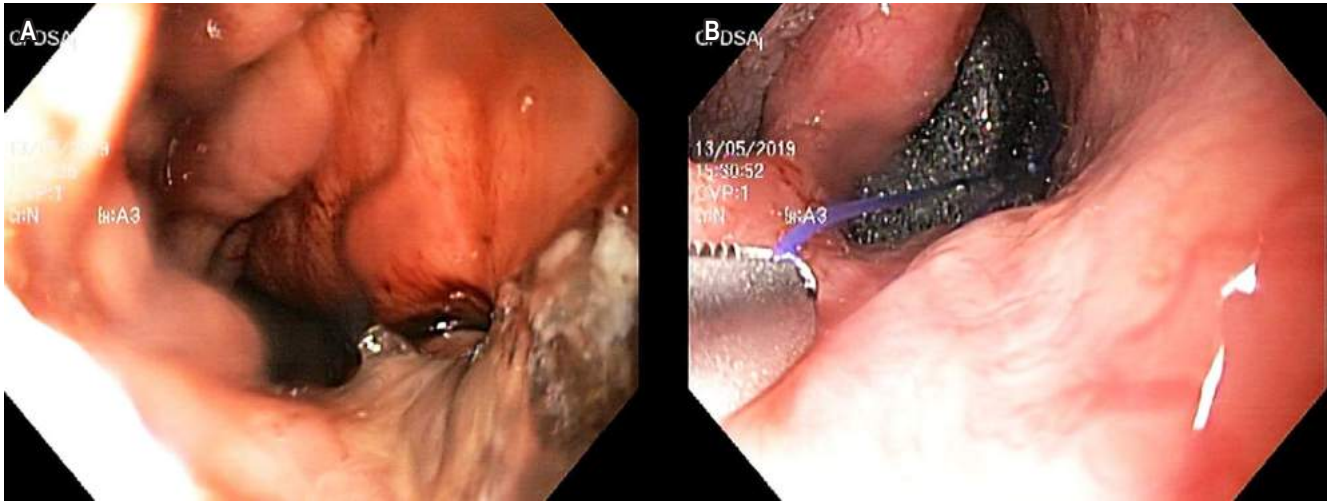


Figure 2. A. Endoscopic visualization of the esophagogastric anastomosis' fistula. **B.** Endo-Vac: Endoscopic insertion of the sponge pulled with suture material using forceps.

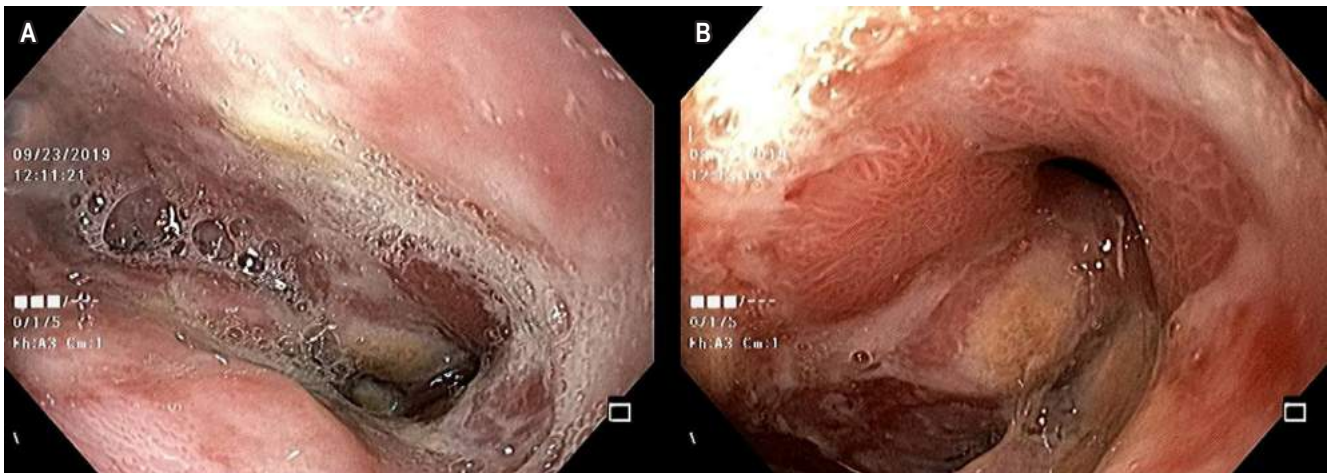


Figure 3. A. Appearance of anastomosis 3 months after completion of treatment with Endo-Vac. **B.** Secondary inflammatory changes.

postoperative anastomotic fistula due to a neoplastic cause. However, failure occurs in 15% of cases and displacement in 40% with complications, such as failed extraction by granulation tissue⁽¹¹⁾ and stenosis at 28.2%. This is a higher rate compared to Endo-Vac therapy (9.4%) ($p < 0.05$)⁽¹²⁾. Additionally, a greater number of days of intensive care unit stay has been described in the stent group compared to Endo-Vac (median 6 vs. 9 days)⁽¹³⁾.

Wedemeyer *et al*⁽¹⁴⁾ reported in 2008 on the endoscopic use of Endo-Vac in the treatment of anastomotic fistula in two patients following an esophagectomy and a gastrectomy. The cavity closure was achieved at 15 days without recurrence. The same results were obtained in the wound healing time in this case. Endo-Vac therapy is an alternative technique that has evolved in managing fistulas for causes

such as sleeve-type gastrectomies, esophageal perforation by transesophageal echocardiogram fistulas in the anastomosis, intraoperative perforation, and Boerhaave perforation. Indications depend on the perforation characteristics, such as a size less than 5 cm, the fistula content, and the absence of cavitations⁽¹⁵⁾.

In 2014, Braun's first endoluminal vacuum sponge Eso-SPONGE® was marketed with a 95% success rate. The technique begins by inserting an overtube after glycerol-based hydrogel has been applied. Then, using a pusher, the Eso-SPONGE® is introduced at the end of the overtube. Once the sponge is in the overtube mark, the overtube is extracted until the pusher handle for releasing the sponge. Both the overtube and the pusher are removed. A nasogastric tube No. 16 Fr is introduced through the nasal cavity

and extracted by mouth. The distal end is cut and connected to the Eso-SPONGE®. Endoscopic control is performed, then it is connected to the vacuum system with a pressure between 50–125 mm Hg⁽¹⁶⁾.

The mechanisms to treat fistula by means of negative or subatmospheric pressure therapy are:

- Exudate control by local modifications in blood flow. Elimination of harmful substances.
- The macrodeformation mediated by the suction on the sponge causes deformation. This exerts the defective edges and unites them.
- Microdeformation is the mechanical changes that occur at the microscopic level and cause the cytoskeleton deformation, the release of growth factors, cell proliferation and migration, and the expression of components of the extracellular matrix.
- Changes in perfusion that increase the microvessels density, hypoperfusion of the defect edges, localized hypoxia, expression of vascular endothelial growth factor, increased angiogenesis (these changes occur between 5 and 8 days), and finally bacterial clearance⁽¹⁷⁾.

DESCRIPTION OF THE PROCEDURE

- *Step 1:* Endoscopic evaluation and characterization of the fistula. Contrast material injection may be used to evidence the leakage under fluoroscopic vision.
- *Step 2:* After evaluating the location and size of the defect, irrigation and endoscopic debridement are recommended. Then, the open-pore polyurethane sponge (VAC® GranuFoam™, pore size 400-600 µm) is trimmed and adjusted to the defect size. Next, at the tip of a nasogastric (NG) polyvinyl chloride tube of 12-14 Fr, additional holes are made with scissors (**Figure 4**).
- *Step 3:* The NG tube is inserted through the nasal cavity and then removed through the mouth with forceps or the finger. The sponge is fixed with a 2/0 suture at the proximal and distal end, leaving the tube in the center of the polyurethane sponge (VAC® GranuFoam™). A short handle is made at its distal end (**Figure 4**).
- *Step 4:* The tip of the tube with the sponge is grabbed from the handle with crocodile forceps and carried endoscopically to the defect site. The entire cavity is



Figure 4. A. Construction of the open-pore polyurethane sponge (VAC® GranuFoam™). Sponge attachment to the end of the NG tube and handle distal loop. B. Insertion of the NG tube (14 Fr) introduced by the nasal cavity with subsequent removal by mouth with forceps.

covered. The sponge should be smaller than the cavity to promote collapse and further closure.

- *Step 5:* After placing the outside of the NG probe, it is taped to the nose. The outer tip is connected to the vacuum system with a continuous negative pressure between 100 and 125 mm Hg.

The average treatment duration with Endo-Vac is 23 days (range between 9 and 86 days)⁽¹²⁾, with a sponge replacement every 3–5 days⁽¹⁸⁾. However, in this study, it was performed every 7 days with a good result. For the replacement or removal of the sponge, the suction must be suspended. Then, the tube is washed with saline solution to separate the granulation tissue. Later, the sponge is retracted and removed. This procedure can be performed endoscopically or directly with further endoscopic revision⁽¹⁹⁾.

The overall success rate of Endo-Vac therapy is 84% to 100%, with an average of 90%⁽⁴⁾. It has also been described that the insertion techniques of the modified Endo-Vac, with the sponge introduction through an overtube, seem to be easier for the endoscopist: a success rate of 100% and procedure time between 12 and 30 minutes⁽²⁰⁾.

Pournaras *et al*⁽⁹⁾ performed a series with 21 patients taken to Endo-Vac. Indications were post-esophagectomy anastomotic fistula, fistula in gastrogastic anastomosis, and iatrogenic esophageal perforation. The cure rate was 95%, and the number of replacements was 3–12. The diagnosis was made 10 days after the intervention, as in the described case, and a jejunostomy was performed in all patients.

In a prospective study of 8 patients with postoperative esophageal fistulas, Endo-Vac was performed on patients with a follow-up of 193 days. It had a successful closure in 88% of cases, mean treatment of 23 +/- 8 days, with no short- or long-term complications. Replacements were made twice a week⁽²¹⁾. Similar to what is presented, the retrospective study by Bludau *et al*⁽²²⁾ reported a success rate in 86% of the cases. Kuehn *et al*⁽²³⁾ reported a success rate in 9 of 11 patients, corresponding to 82% of patients with fistula in anastomosis. The average distance of the lesions was 32 cm from the dental arches, similar to that described in the present case. If there was evidence of mediastinal or intrapleural lesion or unfavorable evolution within 24 hours after the Endo-Vac procedure, follow-up with tomography was indicated.

Following the failed Endo-Vac therapy, complementary management with self-expandable metallic stents partially coated on the Endo-Vac has been described, with a 71.4% first-line success rate and 80% second-line success rate, without serious adverse events⁽²⁴⁾. Brangewitz *et al*⁽¹²⁾ compared the Endo-Vac with the metallic or plastic prosthesis in the closure of esophageal fistulas with a success rate of 84.4% compared to 53.8% in the stent group. There were no differences in hospital stay nor in mortality, but a greater presentation of stenosis in the stent group.

Choi *et al*⁽²⁵⁾ included 39 patients in their study. Eleven cases were treated with Endo-Vac (7 of these cases were switched from stent to Endo-Vac as there was no improvement), and the self-expandable metallic stent was performed in 28 cases, with a median follow-up of 19 months. The Endo-Vac's success rate was 100%, and the self-expandable metal stent's was 74.3% (26/35), with no statistically significant differences. One case presented leak-related death due to infectious complications in the stent group. There were differences in the duration of minor therapy in Endo-Vac compared to the stent (15 vs. 36 days; $p < 0.001$). Complications such as stenosis occurred in 14.3% of the stent group, a higher rate compared to Endo-Vac, 9.1%. No differences were found in the patients' weight, considering that parenteral nutrition is used in Endo-Vac until the sponge removal, and enteral nutrition in the stent is started within 1 to 2 days of insertion.

The disadvantages are periodic endoscopic intervention, permanent connection to the vacuum pump, and oral feeding delaying until the fistula closure⁽²⁶⁾. Excessive granulation stenosis in 5% to 9.1%, responding to endoscopic dilation, has been described as a complication⁽¹³⁾.

CONCLUSION

Endo-Vac therapy is an easy, safe, and effective technique in treating esophageal and gastric anastomosis fistulas as an alternative to the initial management with stents or clips. This allows the closure of fistulas with an excellent success rate, a low rate of complications, such as stenosis susceptible to endoscopic management and reduced hospital stay.

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Intestinal Perforation and Perianal Ulcer Due to Parasitic Infection

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Abstract

Balantidium coli is the largest protozoan and the only ciliated parasite that infects humans. It causes balantidiasis, a disease humans acquire by fecal-oral transmission from its usual host: the pig. We report the case of an immunocompetent schoolgirl who presented with peritonitis due to intestinal perforation, with perianal ulceration secondary to polyparasitism caused by *Balantidium coli*, *Enterobius vermicularis*, and *Trichuris trichiura*. It is a rare, potentially preventable complication with extremely high mortality rates. The patient required eight surgical interventions.

Keywords

Intestinal perforation, balantidiasis, *Balantidium*, parasites, pediatrics.

INTRODUCTION

Balantidium coli (*B. coli*) is the largest protozoan and the only ciliated parasite that infects humans⁽¹⁾. Its distribution is global, but the greatest burden of infection is provided by developing countries⁽²⁾. In the Americas, most cases are reported in Central and South America⁽³⁾. The pig is the main animal reservoir, so the infection predominates in places where the man has close contact with pigs, a situation related to insufficient access to basic sanitation^(2,3). The disease caused by this protozoan is called balantidiasis^(2,4). We report the case of a schoolgirl who presented an intestinal

perforation with perianal ulceration due to *Balantidium coli*, *Enterobius vermicularis*, and *Trichuris trichiura* coinfection.

CLINICAL CASE

A 7-year-old girl from a rural Indigenous community in Chocó, Colombia. She lives with her parents and 12 siblings in a dirt floor house with no electricity or drinking water services. The drinking water is directly obtained from the river. Unpasteurized dairy products are drunk, and pigs are raised. The patient was consulted for a 5-day-evolution clinical picture of subjective fever, diarrheal stools, and

abdominal pain. After being evaluated in the local hospital, she was referred with a suspected diagnosis of dengue with warning signs. She was admitted in a septic shock status with an acute abdomen, so treatment with piperacillin-tazobactam was initiated. The initial blood count reported leukocytes 5000/ul, neutrophils 3900/ul, lymphocytes 800/ul, eosinophils 0/ul, hemoglobin 9.4 mg/dL, hematocrit 28.1%, platelets 60 000/ul, C-reactive protein (CRP) 22.8 mg/dL, and non-reactive HIV ELISA.

An exploratory laparotomy was performed, and fecal peritonitis caused by cecum perforation of the transverse colon (near the splenic flexure) was found, as well as 80% involvement of the ascending colon circumference by multiple microperforations. A right hemicolectomy was performed, with ileum resection at 5 cm from the ileocecal valve to the hepatic flexure, leaving the abdomen open. The patient was sent to the pediatric intensive care unit with vasopressor support. Intravenous metronidazole was added to the treatment. A perianal ulcer of 2 x 2 cm with a fibrin-covered bottom (**Figure 1**) was evidenced.



Figure 1. Perianal ulcer on admission to the institution. Approximate size of 2 x 2 cm. Note the disappearance of the anal sphincter's anatomical relationships.

The patient was intervened after 2 days. Multiple perforations in the transverse colon and at a splenic flexure were found, with a collection in the right and subhepatic parietocolic gutter, ischemia points in the tapeworm, and antimesenteric border of rectosigmoid junction. A subtotal colectomy was performed with transverse colon, distal ileum, and sigmoid colon resection. The ileostomy was left. On day 5 of hospitalization, punctiform perforation raffia and peritonitis drainage were performed. On day 7, adhesions were released, and the intestine was repositioned in

the abdominal cavity. A pathology report from colon samples taken in the first intervention was obtained. Parasitic infection by *Balantidium coli* (**Figure 2**)⁽⁵⁾ was confirmed, in addition to helminthiasis consistent with trichocephalus and pinworm. The patient had already received 7 days of metronidazole, so treatment for helminths with ivermectin (2 doses) was indicated by infectiology.

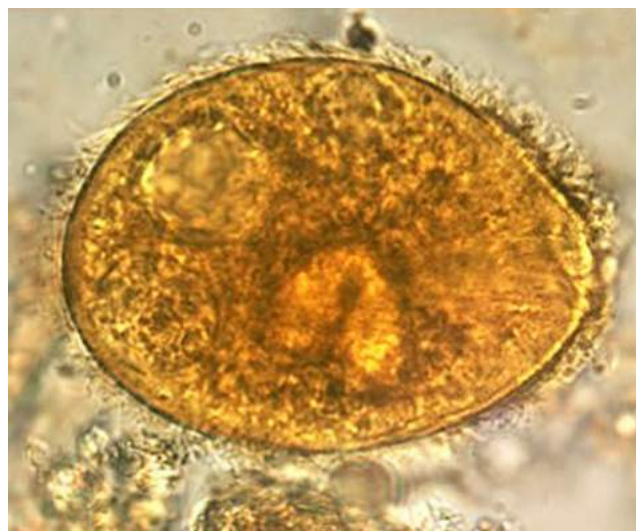


Figure 2. *Balantidium coli*: A trophozoite in a droplet of feces. Magnified x 1000. Note the visible cilia on the cell surface⁽⁵⁾. Image taken from⁽⁵⁾.

On day 10 of hospitalization, an exploratory laparotomy was carried out. Abdominal wall fasciitis, contained evisceration, ileostomy with fistula, and distal perforation of the wall were found. The abdomen was left open, and the perianal ulcer was debrided. After this intervention, there was clinical deterioration. An extension of the antibiotic spectrum to meropenem and vancomycin was required.

On day 15 of hospitalization, surgical lavage was carried out with vacuum-assisted closure (VAC) placement and mesh. A colon swab culture was obtained with yeast findings consistent with candida, so fluconazole was added to the treatment. The patient underwent surgery two more times. Final closure of the abdominal wall was achieved. The enteral route was then restarted, and oral metronidazole was received for 7 days. The perianal ulcer was healing with advanced cures using fitostimuline and hydrofiber dressings with silver. After 36 days of hospitalization, the patient was discharged with ileostomy, oral feeding tolerance, and multidisciplinary follow-up (**Figure 3**).

DISCUSSION

Balantidium coli is the only ciliated protozoan known as a human pathogen. Its trophozoite is 50 to 200 µm in length and 40 to 70 µm in width. This microorganism causes



Figure 3. Perianal ulcer in medical checkup. The exposed tissue disappeared. It is now epithelialized, and its size has decreased.

balantidiasis, a zoonotic disease acquired by humans via fecal-oral transmission from its usual host: the pig. Contaminated water with porcine or human feces infecting cysts is its main vehicle, although it can also be acquired from person to person^(1,2).

The main risk factors for infection include close contact between pigs and humans, inadequate sanitation, and subtropical or tropical climates, which favor the parasite survival in the form of an infectious cyst^(2,3).

There are few reports in Latin America. A study in Bolivia examined more than 2000 stool samples in an asymptomatic population aged 5–19. *B. coli* was detected in 1.2% of cases⁽⁶⁾. Colombia has no prevalence records of this infection, but studies have been conducted on the Caribbean Coast. For example, Urbina *et al* identified *Balantidium coli* in 0.8% of children with acute diarrhea⁽⁷⁾.

The parasite has two forms: trophozoites, usually identified in dysenteric feces, and cysts in formed feces and chronic carriers. It is replicated by binary fission or sexual reproduction⁽²⁾. It inhabits the large intestine in humans and can remain there without invading tissues or causing clinical disease^(1,8). In fact, most infections are asymptomatic or occasionally cause acute diarrheal disease, a situation that accounts for 85% of patients who harbor the protozoan. This clinical form is more common in children than adults⁽⁹⁾. Less commonly, it can manifest with intermittent diarrhea, abdominal pain, and weight loss⁽¹⁾.

In some cases, *Balantidium coli* can cause serious disease with dysentery, secondary to tissues destruction by

invading the colonic mucosa. Along with hyaluronidase release, it causes ulcers and microabscesses associated with a polymorphonuclear inflammatory infiltrate^(1,2,10). This condition favors bacterial overgrowth, worsening the clinical picture⁽¹¹⁾. Cases of extraintestinal dissemination have also been described in adults with genitourinary, pulmonary areas^(12,13), and even vertebral osteomyelitis⁽¹⁴⁾, patients with immunosuppression^(12,13), malnutrition^(2,9), a history of excessive alcohol consumption⁽¹⁵⁾ or polyparasitism⁽²⁾.

Surgical intervention is required when invasive gastrointestinal complications such as typhlitis, appendicitis, and peritonitis occur⁽⁹⁾. Colon perforation is a sporadic complication associated with extremely high mortality rates^(1,3,16). Although the patient survived, she presented significant morbidity. She was taken to 8 surgical interventions with a complete colon resection, and a terminal ileostomy was necessary.

The treatment of choice for children over 8 years old is oral tetracycline at 40 mg/kg per day, divided into 4 doses for 10 days (maximum 2 g/day)⁽¹⁷⁾. As an alternative, since our patient was under 8 years of age, oral metronidazole was indicated in doses of 35–50 mg/kg/day, divided into 3 doses for at least 5 days⁽¹⁷⁾. However, it was not possible to start this treatment orally due to the patient's condition. She received an initial intravenous cycle and then the oral one, which was successful. Another alternative is iodoquinol, 30 to 40 mg/kg per day (maximum 2 g) in 3 doses for 20 days⁽¹⁸⁾. Nitazoxanide may also be effective⁽²⁾. The literature reports other antibiotic agents that have been tested with variable success, such as paromomycin and chloroquine⁽¹⁹⁾.

In 2014, the “Clinical Practice Guide for the Promotion, Early Detection and Initial Approach of Growth and Developmental Disorders in Children”⁽²⁰⁾ was published in Colombia. This guide recommends preventing intestinal parasitism in children with any epidemiological risk factor: food intake or contaminated water, life in rural areas, poor hygiene and education, human migrations, and poor socioeconomic and health conditions. Some of these factors were identified in our patient. According to this guideline, these children should receive a single dose of albendazole, 400 mg orally. Although this drug is not recommended for the treatment of *Balantidium coli*, it is the first-line treatment of *Enterobius vermicularis* and *Trichuris trichiura*. It is likely that if albendazole had been administered with the semi-annual frequency established in the protocol, the girl would have had less risk of the presented outcomes. Thus, parasitic co-infection, one of the factors described in severe infections, would have been avoided.

This case provides evidence of the role of *B. coli* as a pathogen in immunocompetent children and of polyparasitism as a risk factor for severe complications,

such as peritonitis with intestinal perforation, which are potentially preventable with deworming in at-risk populations. This is the first case reported in Colombia.

CONCLUSIONS

Infestation by intestinal parasites is common in children who do not have drinking water and live in poor health conditions, with chronic or recurrent diarrhea and abdominal pain as the predominant clinical manifestation. Perianal ulcers and intestinal perforation from parasitic causes are rare. Intestinal polyparasitism has a negative impact on the nutritional status of children. This, in turn, directly affects the tissue's repair capacity so that intestinal ulcers can take longer to heal. The infestation by multiple parasites in the same patient can also favor a greater severity

in symptoms since the pathogenicity mechanisms of each agent will be summative. It is important to guarantee the drinking water supply to at-risk populations, improve environmental sanitation conditions, diagnose and timely treat parasitic diseases, and correct the children population's nutritional deficiencies, thus achieving their well-being and potential psychomotor, cognitive, and social development.

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Lymphomatous Polyposis: Case Report and Literature Review

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Abstract

Lymphomatous polyposis (LP) is the endoscopic feature of primary gastrointestinal mantle cell lymphoma (MCL), a rare type of B-cell non-Hodgkin's lymphoma (NHL) and a typical but rare endoscopic pattern of gastrointestinal tract involvement (GIT) by nodal MCL. We present the case of a 62-year-old man with nodal MCL, with LP as a manifestation of GIT, and review the literature.

Keywords

Lymphomatous polyposis, mantle cell lymphoma, gastrointestinal tract.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) of the gastrointestinal tract (GIT) is the most common extranodal lymphoma. Approximately 15%–30% of primary extranodal lymphomas occur in the GIT. Mantle cell lymphoma (MCL) accounts for 3%–6% of all NHL. It has a heterogeneous biological and clinical behavior and is frequently diagnosed at an advanced stage^(1,2).

Lymphomatous polyposis (LP) is a rare endoscopic finding that, although described typically in patients with primary and extranodal GI MCL, with GIT infiltration, is not specific to this type of lymphoma. It has also been described in patients with follicular lymphoma and mucosal-associated lymphoid tissue (MALT). LP is character-

ized by multiple polypoid lesions involving long segments of the GIT^(3,4).

We present the case of a patient with LP as an endoscopic manifestation of secondary involvement of the GIT by extranodal MCL. This case report was made following the case report guidelines (CARE)⁽⁵⁾.

PRESENTATION OF THE CASE

A 62-year-old man with a history of hypertension (HT). He was admitted to the emergency room for a 4-month evolution clinical picture, consisting of non-painful adenopathies in the neck and inguinal region with progressive growth. During the last 2 months, he associates voice tone changes, mMRC 3 dyspnea, nocturnal diaphoresis with

decubitus, oropharyngeal dysphagia for solids, and a 20 kg weight loss. On physical examination, the presence of up to 2 cm hard adenopathies is palpated in cervical, axillary, and inguinal lymph node chains. Bigger palatal tonsils are also felt. Initial paraclinical tests showed lymphopenia (900 μ L) with no other abnormalities.

A contrasted tomography (CT) scan of the neck, abdomen, and pelvis suspecting lymphoproliferative disorder is performed. Tonsillar hypertrophy, which conditions the closure of 70% of the oropharynx, was found. Also, extensive involvement of adenopathies was found in cervical, axillary, and mediastinal lymph node chains, a subcarinal nodal conglomerate obstructing the main and retroperitoneal bronchi and gastric walls thickening (**Figure 1**).



Figure 1. CT scan of the contrasted abdomen. Thickening of the gastric walls of predominance in the gastric fundus.

Upper gastrointestinal endoscopy (UGIE) with severely enlarged palatal tonsils, edematized esophageal mucosa, thickening of gastric folds, and presence of multiple polypoid, vascularized lesions, some superficially ulcerated between 2 and 25 mm (**Figure 2**).

The esophagus, stomach, and duodenum histopathological study reveal an extensive infiltrate by atypical, mature, small-sized, and monotonic lymphocytes in the lamina propria. CD20, CD5, D1 cyclin, and bcl-2 positive with a 60% ki-67 in the immunohistochemical study with a compatible infiltration by classical MCL variant (**Figure 3**). Excisional biopsy of the cervical lymph node with similar findings. Bone marrow (BM) with 10% infiltration.

In a patient with nodal MCL, GIT and BM extranodal involvement, an intermediate risk mantle cell lymphoma international prognostic index (MIPI), and risk of complete

airway obstruction by amygdalin infiltration, a systemic steroid was administered in the prephase. Then, chemotherapy was administered using the R-CHOP scheme (rituximab + cyclophosphamide + vincristine + doxorubicin + prednisone) interspersed with R-DHAP (rituximab + dexamethasone + cytarabine + platinum). The patient is currently in the fourth cycle of chemotherapy. Peripheral adenopathies have disappeared, and the tonsils' size is now normal.

LITERATURE REVIEW

MCL is a rare subtype of mature B-phenotype NHL. This represents 3%–6% of NHL. It predominantly affects men (2–3:1), and the mean age at diagnosis is 68 years^(1,2). At the time of diagnosis, 75% of patients present an advanced stage, with generalized lymphadenopathy, bone marrow, and GIT involvement⁽¹⁾. GIT is the most affected extranodal site by peripheral MCL. There is microscopic involvement in 88%–92% of cases, but only 25% of patients present GI symptoms^(3,4,6,7). Endoscopic findings are variable and include polypoid lesions, granular patterns, superficial ulcers, diffuse infiltration of the GI wall, and nonspecific mucosal changes such as edema^(4,8).

LP was first recognized two centuries ago. However, it was described and reviewed for the first time in 1961 by Cornes *et al*⁽⁹⁾ as the primary GI involvement of the MCL. It accounts for 4% to 9% of primary GI B lymphomas and is originated from the mantle area of lymphoid follicles^(1–3). The main presenting symptoms are abdominal pain, diarrhea, and hematochezia. Weight loss, night sweats, and fatigue are also common⁽¹⁰⁾. The endoscopic finding consists of multiple polypoid lesions of 2 mm, up to several centimeters in diameter, with or without interspersed normal mucosa in one or more GIT segments. The proliferation of monomorphic small-to-medium size lymphocytes is characteristic of this polyposis, and in the study of immunohistochemistry like CD20+, CD5+, CD23-, with overexpression of chromosomal translocation t(11;14) and D1 cyclin⁽³⁾. It most often affects the ileocecal region, ileum, stomach, and duodenum^(10,11).

PL is the typical (uncommon) endoscopic pattern of GIT involvement by nodal MCL^(3,4,8,12). Esophageal involvement by MCL is unusual due to the low number of lymphoid cells^(3,13). Although GI involvement by MCL typically occurs as LP, this is not a specific finding of MCL. It has also been described in cases of T-cell NHL, follicular lymphoma, MALT, and diffuse large B-cell lymphoma^(3,4).

Primary GIT involvement by MCL in the form of LP has prognostic implications. It presents aggressive biological behavior and implies a median survival of 3 to 4 years^(3,4,6,12). In contrast, GIT evaluation, as disease staging

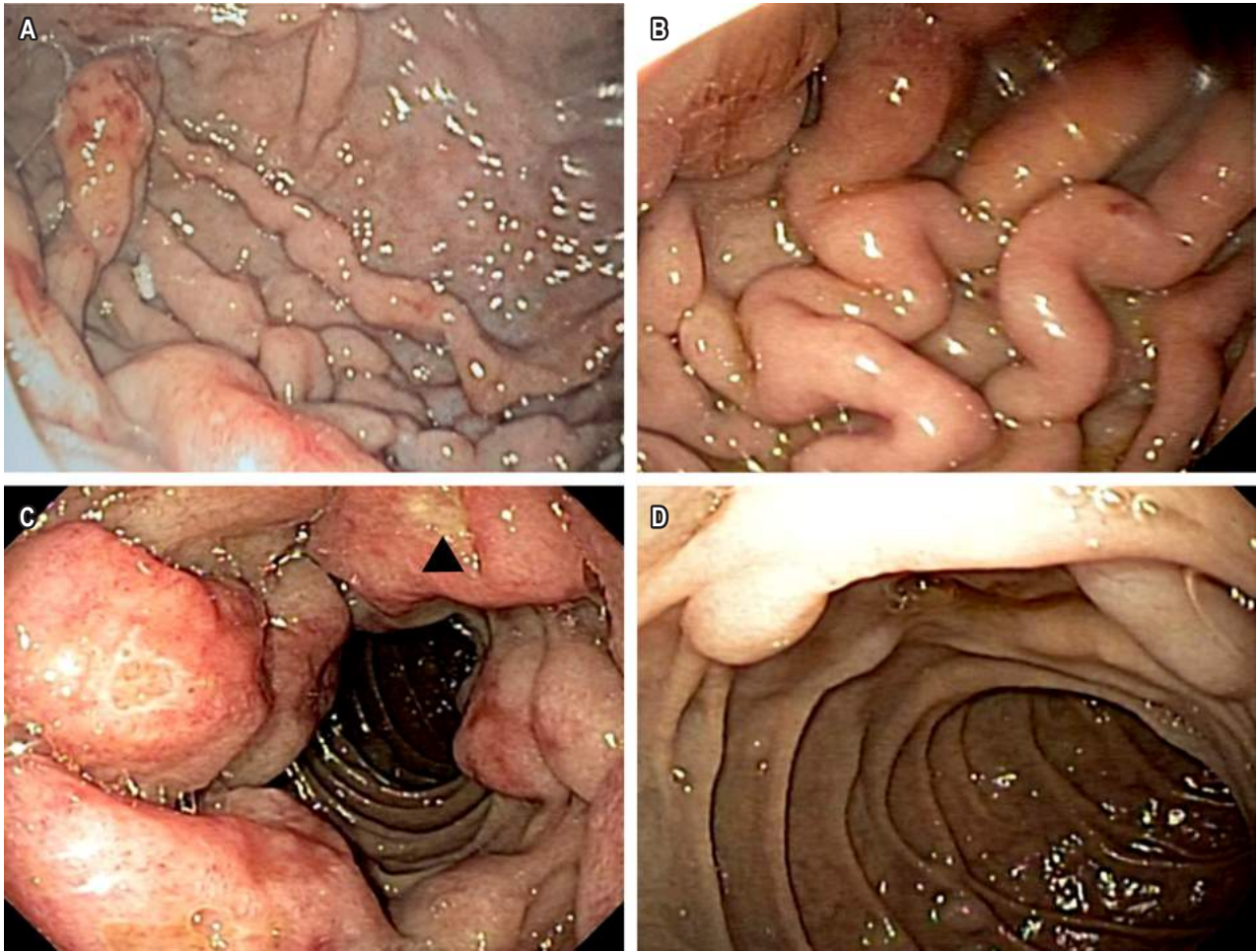


Figure 2. Upper gastrointestinal endoscopy **A.** Polypoid lesions on the gastric fundus. **B.** Severe thickening of gastric folds. **C.** Polypoid lesions with circumferential involvement of the duodenal bulb. Ulcerated lesion (Δ). **D.** Polypoid lesions of variable sizes in second duodenal portion.

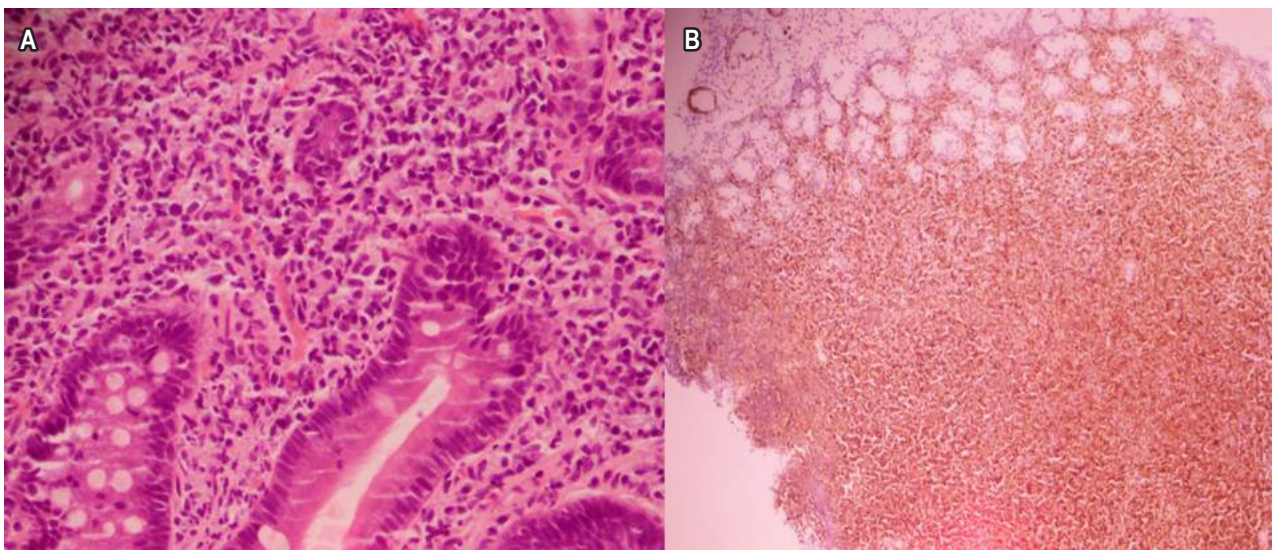


Figure 3. Histopathology and immunohistochemistry. **A.** Duodenal infiltration by small lymphocytes, monotonic (hematoxylin-eosin staining, 40x). **B.** Positive nuclear labeling for D1 cyclin (40x).

in patients with confirmed nodal MCL, has little impact on therapeutic decisions^(1,3,4,6).

Treatment of LP involves the management of lymphoma. There is variability in clinical practice around the therapeutic approach to MCL. In general terms, the choice of treatment scheme is based on the patient's characteristics (age, comorbidities, functional status), symptoms, staging, and safety profiles of the schemes. Chemoimmunotherapy, followed or not by consolidation with autologous hematopoietic cell transplant, is the usual approach^(1,2).

CONCLUSIONS

GIT is the most frequently extranodal site affected by peripheral MCL. LP is a rare endoscopic manifestation of this and other types of NHL. It should be considered in the differential diagnosis for multiple polyposis of the GIT.

Conflicts of interest

The authors do not declare conflicts of interest.

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Case Report of a Metastatic Biliary Tract Neoplasm as an Unusual Cause of Appendicitis

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Abstract

Introduction: We describe the case of a patient with appendiceal metastasis as the first manifestation of a cholangiocarcinoma. Main symptoms: Abdominal pain, jaundice, hyporexia, and choloria. **Methods and results:** We documented an appendiceal plastron histologically compatible with metastatic appendiceal adenocarcinoma, common hepatic duct stricture, and a suspected cholangiocarcinoma, later corroborated by endoscopic retrograde cholangiopancreatography. **Conclusions:** Metastatic appendiceal tumors are an infrequent and poorly studied manifestation, whereas those secondary to bile duct neoplasia have rarely been reported in the literature.

Keywords

Appendix, metastasis, cancer, cholangiocarcinoma, adenocarcinoma.

INTRODUCTION

Appendiceal tumors are a rare entity with a reported incidence between 0.1% and 17%⁽¹⁾. One of the main situations that slow down the diagnosis of this pathology is its similarity to appendicitis. The neoplasm obstructs the appendiceal orifice, leading to obstruction and an acute inflammatory process⁽²⁾. This is a concern as appendiceal tumors may go unnoticed, increasing their incidence.

Most of these cases are evidenced in appendectomies with atypical intrasurgical findings such as appendicular plastrons or masses with neoplastic characteristics non-

consistent with appendicitis only⁽³⁾. Appendix neoplasms secondary to metastatic involvement are also less common. The literature reports that secondary malignant involvement of the appendix is, within these cases, more common due to the direct extension of colon carcinoma, pelvic neoplasms and less frequent due to distal metastasis⁽⁴⁾.

CASE REPORT

This is a 65-year-old male patient from Cartagena, Bolívar, Colombia. He consulted for a 15 day-of-evolution clinical picture consistent with abdominal pain in the right iliac

fossa, jaundice, choluria, unintentional weight loss, and hyporexia.

The patient has no relevant pathological history. He has a surgical history of right inguinal herniorrhaphy without documented complications or previous pharmacological management. He was admitted with generalized abdominal pain (especially in the right iliac fossa), signs of peritoneal irritation, and generalized jaundice.

A laparoscopic appendectomy and biliary bypass by endoscopic retrograde cholangiopancreatography were required with the insertion of a biliary stent in the referral hospital. Intraoperative finding of an appendicular plastron, abundant serous peritoneal fluid, narrowing of the common hepatic duct, with suspicion of neoplastic involvement. The patient was transferred to Hospital Militar Central in Bogotá, Colombia, to continue with comprehensive management. The obstructive biliary syndrome was documented with a total bilirubin count of 3.02 mg/dL, direct bilirubin of 2.71 mg/dL, alkaline phosphatase of 1006 IU/L, alanine aminotransferase (ALT) of 149 U/L and aspartate aminotransferase (AST) of 139 U/L. The magnetic resonance (MR) cholangiography findings are presented in **Figure 1**, and those from the computed axial tomography (CT) in **Figure 2**. The result of the appendicular biopsy showed

compromise due to moderately differentiated adenocarcinoma of serous and muscle layer (**Figure 3**), positive immunohistochemistry for CK7, EMA, monoclonal CEA, and CDX2 antibodies (**Figure 4**). This suggested an extra-appendicular origin, probably from the upper or hepatobiliary gastrointestinal tract.

The patient was taken back to endoscopic retrograde cholangiopancreatography, evidencing type IV Klatskin tumor. A 10 x 10 French (Fr) stent was inserted in the right hepatic duct and another 12 x 10 Fr stent in the left hepatic duct. Antibiotic coverage with piperacillin/tazobactam was also initially indicated for 72 hours. However, cholangitis was diagnosed given the persistence of obstructive biliary syndrome and fever onset. Therapeutic stepping to meropenem and biliary bypass by interventional radiology were required.

The oncology service proposed to initiate palliative chemotherapy once bilirubin reached under 3 mg/dL. After the first cycle of chemotherapy, the patient was discharged to continue with outpatient management.

DISCUSSION

This report presents the case of a patient with an unusual appendiceal tumor because it began as abdominal pain,

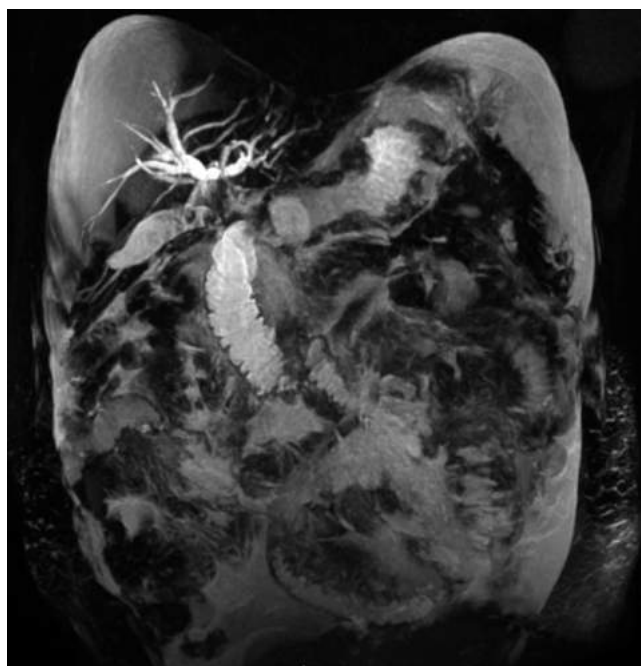


Figure 1. 3D MR cholangiography. Intrahepatic bile duct dilation. Abrupt transition and thready liquid flow into the common hepatic duct are observed in the right and left hepatic ducts. Distended gallbladder with multiple hypointense images and interior perigallbladder fluid.



Figure 2. Cecal appendix with contrast material in its lumen, periappendiceal fat stranding, and, in contact with its vertex, heterogeneous mass of poorly defined contours with hypodense and dense areas of 35 x 32 x 44 mm.

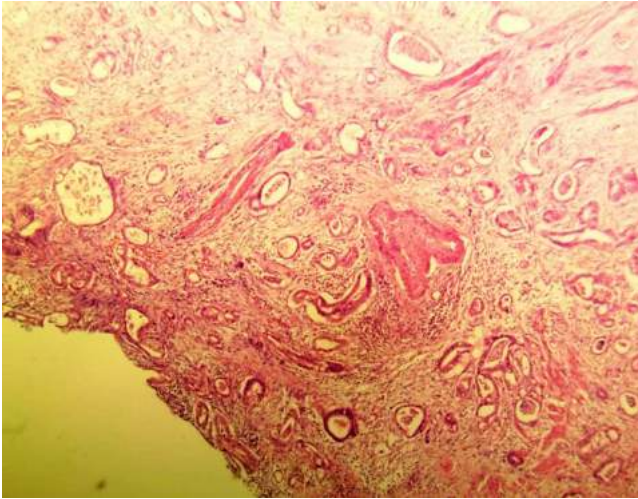


Figure 3. Microscopic findings of the surgical specimen. Hematoxylin and eosin staining show multiple tumoral cells infiltrating the appendiceal serous layer to the submucosa.

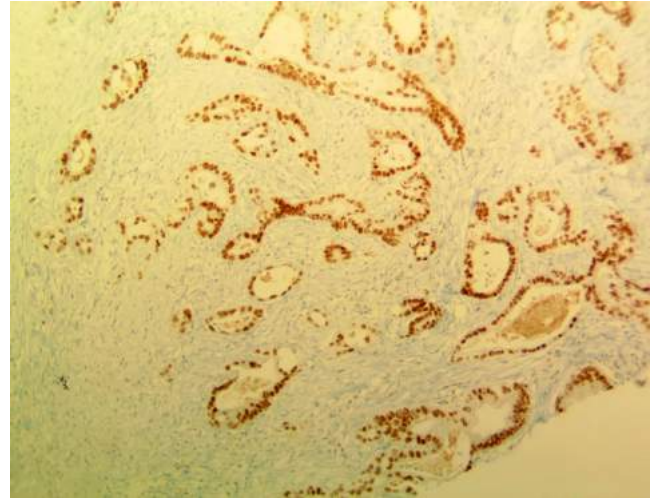


Figure 4. Immunohistochemistry of surgical material, positive for CK7.

typically characterized as inflammatory appendicitis. However, intraoperative and later anatomopathological findings showed an appendix metastatic cholangiocarcinoma, an unusual presentation in the literature.

Most appendiceal tumors are epithelial neoplasms and neuroendocrine tumors⁽⁵⁾, being less frequent metastatic tumors, lymphomas, neuroectodermal, mesenchymal tumors, and Kaposi's sarcoma⁽⁶⁾. In a review of the literature, which retrospectively evaluated the histopathological findings of appendectomies, only 7 patients showed metastatic compromise out of 80,698 patients⁽⁷⁾. This is a significant figure that puts into perspective the unusualness of this presentation. The bile duct was not reported in this study's primary sites of metastasis. This situation was atypical for the presentation⁽⁸⁾.

A case report denoted an appendix metastatic cholangiocarcinoma in a patient with the obstructive biliary syndrome, abdominal pain, and jaundice⁽⁹⁾. However, the appendiceal finding in this patient was derived from previously performed imaging studies, such as a contrasted computed tomography, which showed cholangiocarcinoma with direct liver extension. Then, a PET scan denoted a mass in the proximal appendix, suggestive of malignancy. This contrasts with the primary intrasurgical finding in the appendectomy in our case.

On the other hand, a case of acute appendicitis with a subsequent finding of appendicular metastatic involve-

ment due to cholangiocarcinoma was also reported in the literature⁽¹⁰⁾, a similar clinical presentation to our case. Nevertheless, radiological findings suggest preponderance by metastatic extension, by contiguity rather than by distant seeding of malignant cells⁽¹¹⁾, which could favor a greater presence of secondary involvement by colorectal cancer than by more distant as bile duct-dependent ones.

More information on the clinical presentation of these patients is needed due to the significant limitation of high-quality evidence in this regard. The heterogeneity of the patients' characteristics on metastatic appendiceal adenocarcinoma reports and, above all, the extreme scarcity of reported cases in the literature do not allow us to infer differences that explain the clinical presentation nor to discern the predictors or prognostic factors of this disease.

We consider that the main strength of this case is the unusual presentation of a metastatic appendiceal tumor of biliary origin, minimally reported in the literature. Likewise, a deep diagnostic exercise and follow-up in a high complexity hospital offer relevant information on the need for and importance of a multidisciplinary approach for patients who present this type of pathology. Given this, it is important to evaluate the presence of similar cases in future studies, which can offer systematized and high-quality information on this clinical presentation.

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Unusual Case Report of Synchronous Caecal and Sigmoid Volvulus

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Abstract

In the spectrum of patients with intestinal obstruction, volvulus is one of the least frequent etiologies (5-15 %). Synchronous volvulus of two colonic segments in a patient is regarded as rare, with few cases reported in the literature. The present report of synchronous cecal and sigmoid volvulus documents one of them: a patient who underwent subtotal colectomy and formation of ileostomy. Although the preoperative diagnosis of this entity is rare, it should be considered in these intraoperative findings for both intraoperative management, with resection and anastomosis or resection and stoma, and postoperative management. It has a significant impact on mortality if patients are treated with broad-spectrum antibiotic coverage, given the bacterial translocation and sepsis that they experience.

Keywords

Intestinal volvulus, sepsis, general surgery.

INTRODUCTION

Intestinal volvuli are considered the cause of intestinal obstruction in 5%–15% of cases⁽¹⁾, although their incidence is believed to increase in the Middle East, Asia, and Africa⁽²⁾ in the geographical area considered the “volvulus belt”⁽¹⁾. This twisting is not frequent in our environment. Synchronous or simultaneous volvuli cases are considered rare⁽³⁾. Few cases are reported in the literature. This case report presents a patient with a cecum and sigmoid colon synchronous volvulus. This is currently one of the few cases reported in world literature.

CASE REPORT

A 48-year-old male patient arrived at the emergency department with his sister. The patient has a cognitive deficit, but his guardian reports 7 days of abdominal distension worsening, associated with hyporexia, having a stool of normal consistency the previous day. There was no fever or apparent pain on admission. Fecal incontinence history without previous studies was reported.

Upon admission, the patient was afebrile, hydrated, tachycardic with a frankly distended, tympanitic abdomen,

and peristaltic noises with decreased tone and frequency. He presents no pain. Digital rectal examination performed with empty rectal ampulla and hypotonic anal sphincter. Abdominal X-rays are performed (**Figure 1**). Clear loop distension is considered (which conditions a critical colon), so urgent surgical intervention is indicated.

Despite decompression with a nasogastric tube, the patient has severe abdominal distension in the operating room (**Figure 2**). A xypho-pubic laparotomy is performed. Upon entering the cavity, two volvuli are found: one of the cecum and the other of the sigmoid colon, devolvulated with vascular pedicle control (**Figure 3A-C**). Distension that conditions a critical colon is found, so a subtotal colectomy plus ileostomy is performed (**Figure 3D**).

The patient is extubated and transferred to the floor with expected clinical evolution. During the immediate postoperative period, 2 packaged red blood cells are transfused. On the second day, the patient has an adequate intestinal transit. The nasogastric tube is removed, and a liquid diet is started. On postoperative day 4, a nursery call is received since the patient has emetic episodes of feculent content with abundant bleeding from the ileostomy. The patient is tachycardic with great abdominal

distension and generalized pain on palpation, so he is urgently taken to the operating room.

During the second surgical procedure, hemoperitoneum is found in the patient without apparent active bleeding or its cause, also a large dilation of thin loops with no transition zone. A non-ischemic permeable ileostomy is left with packaging. After 2 days, a new surgical procedure is carried out having turbid peritoneal fluid with fibrinopurulent membranes in thin intestinal loops. The wall is closed, but the patient requires vasopressor and invasive ventilatory support because extubation is not possible. The patient is transferred to the intensive care unit.

The patient evolves in very bad general conditions with vasopressor support in high doses and oligoanuric. He presents multiorgan dysfunction associated with septic diseases, which does not respond to medical or antibiotic management, and dies.

DISCUSSION

The term volvulus is derived from Latin *volvere* “rotate on its own axis”⁽¹⁾. It was first described in the Ebers papyrus in 1550 BC with a description of the natural course of the

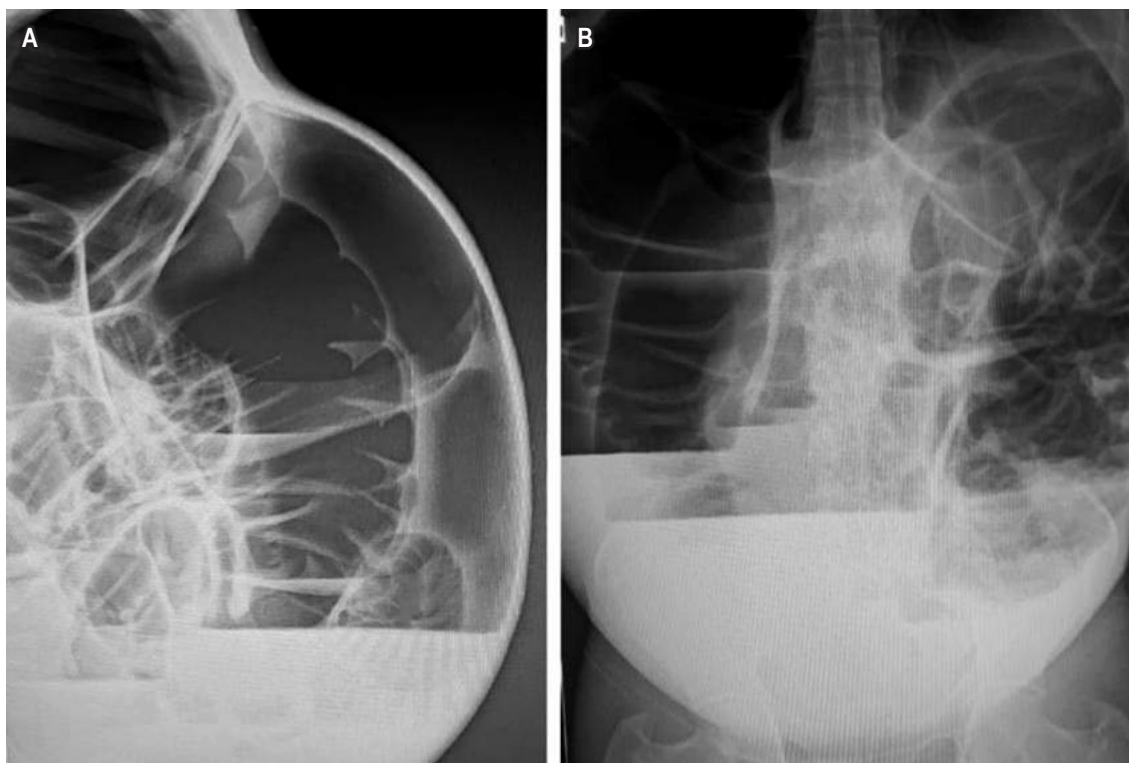


Figure 1. Abdominal X-rays in standing position. **A.** Lateral view. **B.** Anteroposterior view.



Figure 2. Photograph of the patient's condition before the procedure started: Clear abdominal distension, despite decompression with a nasogastric tube and urinary catheter.

volvulus with spontaneous torsion and intestinal reduction or rotting⁽¹⁾. The presentation of each volvulus is considered an independent entity⁽³⁾. Volvuli are more common in the sigmoid colon (75%) and the cecum (15%–22%)⁽⁴⁾. However, there are reports of volvuli in the transverse colon (3%) and the splenic flexure (2%)⁽⁴⁾.

The double colonic volvulus has been considered a rare entity⁽³⁾. The literature records this presentation as synchronous volvuli, compound volvuli, simultaneous volvuli, or double volvulus. Singh *et al* documented the first case in 1985⁽⁵⁾. There are also reports by Theuer *et al* (1991)⁽⁶⁾, Moore *et al* (1992)⁽³⁾, Kellil *et al* (2017)⁽⁷⁾, and Islam *et al* (2016)⁽⁴⁾.

Volvuli occur mainly in the Middle East, Asia, and Africa^(2,3). This zone is known as the “volvulus belt”⁽¹⁾ in the literature, which is associated with a fiber-rich diet. Additionally, other risk factors are considered: a long and mobile mesentery, redundant sigmoid, and chronic intestinal distension⁽²⁾. Likewise, there are individualized risk factors for each of its presentations. The sigmoid volvulus is related to a fiber-rich diet, previous abdominal surgery, psychiatric disorders, Chagas disease, Parkinson's disease, ischemic colitis, and megacolon⁽³⁾. Additionally, it frequently affects the elderly population in nursing homes and patients with neurological pathologies⁽³⁾.

Symptoms include abdominal pain (100%), abdominal distension (94%–100%), nausea and vomiting (87%–100%), and rebound tenderness (69%)⁽²⁾. However, it is not an easily pre-surgically diagnosed condition. Only 20% of patients are diagnosed⁽²⁾.

Timely management is essential in these patients. Compromised blood circulation leads to a rapid progression of necrosis of the volvulated segments (75%–79%), which can be life-threatening⁽³⁾. These patients must receive aggressive fluid resuscitation, broad-spectrum antibiotics, and definitive surgical management^(4,6). According to the intraoperative findings and the patient's conditions, it is decided whether the patient benefits from resection and anastomosis or whether a terminal ostomy and delayed anastomosis should be performed^(2,3).

Complications in these patients are associated with peritonitis, sepsis, and dehydration because of the third spaces generated⁽²⁾. Although described at 15%, mortality can be as high as 73% of cases. It is associated with septic shock, caused by bacterial translocation and intraoperative colon manipulation⁽²⁾.

CONCLUSION

Synchronous presentation of intestinal volvuli is an uncommon occurrence in patients with intestinal obstruction. It is an intraoperative diagnosis performed in a patient undergoing a surgical abdomen procedure in most cases. These patients' management should be based on their conditions. However, the septic commitment and broad spectrum of antibiotic coverage that must be received in the postoperative period associated with strict clinical and paraclinical monitoring should be considered.

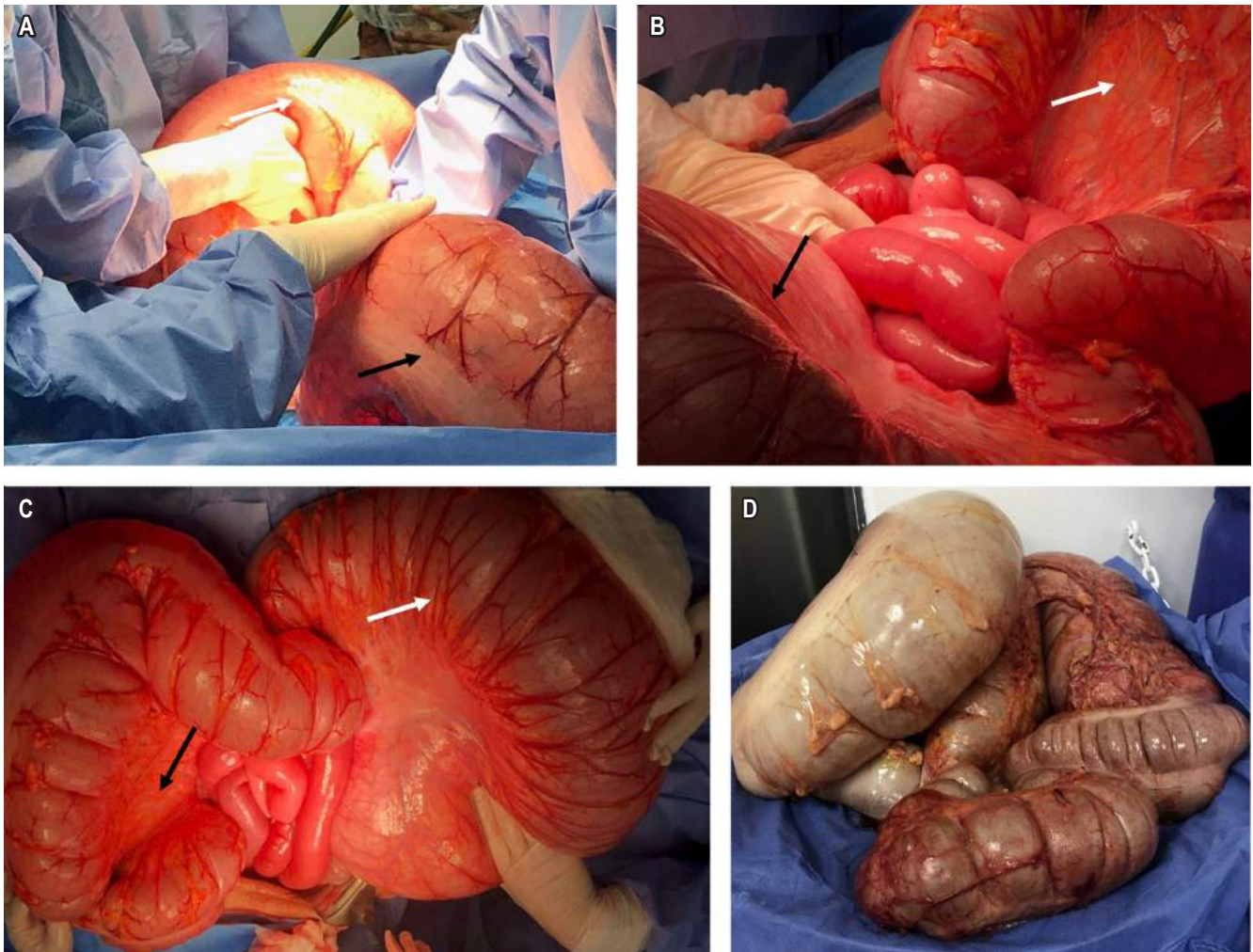


Figure 3. Intraoperative images. **A.** Synchronous volvulus of the cecum (white arrow) and sigmoid (black arrow). **B and C.** Results of the devolvulation: sigmoid (white arrow) and cecum (black arrow). **D.** Product of subtotal colectomy, surgical specimen.

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Disseminated Abdominal Echinococcosis: Case Report

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Abstract

We describe a case of disseminated abdominal hydatid disease in a 21-year-old man who presented with clinical symptoms of persistent abdominal pain after abscess drainage post-appendectomy. The images showed multiple cystic lesions in the peritoneum, liver, and spleen. Due to pain exacerbation, the patient was taken to laparotomy. Multiple cystic lesions scattered throughout the abdominal cavity were observed, which were diagnosed by histopathology as multiple cystic lesions due to peritoneal and abdominal echinococcosis.

Keywords

Echinococcosis, hydatidosis, abdominal, diagnosis, treatment, follow-up.

INTRODUCTION

Although echinococcosis has a long history dating back to ancient times, it is still a relevant zoonosis nowadays. It has a considerable socioeconomic impact and affects humans worldwide⁽¹⁾. This is a disease caused by parasites, specifically the cestodes of the genus *Echinococcus*⁽²⁾. Two of the most important forms (which have medical and public health significance) are cystic echinococcosis (hydatidosis), caused by infection by *E. granulosus*, and alveolar echinococcosis, caused by *E. multilocularis*⁽²⁾.

Cystic echinococcosis has a worldwide distribution. There are endemic foci in all inhabited continents. The highest prevalence of this disease has been found in temperate zones: Mediterranean countries, southern and cen-

tral Russia, Central Asia and China, and some regions of Australia and America (especially South America). Some risk factors for getting this disease include low socioeconomic status, scarce health education, living in rural areas, and the relationship with dogs in contact with livestock or animal offal⁽³⁾. Although it does not have high mortality (2.2%), it does have high morbidity and an economic impact of billions of dollars⁽³⁾.

E. granulosus requires two mammalian hosts to complete its life cycle: a definitive host (carnivore, especially the dog), where the adult phase is developed, and an intermediate host (sheep, goats, pigs, cattle, among others), where the larval phase or hydatid cyst is spread. Infection in man occurs after parasite eggs are ingested by accident. The eggs reach the small intestine, where their cover is dissol-

ved. Embryos that cross the intestinal mucosa are released and pass into the venous circulation to reach the different organs. They are often in the liver (67%–89%), followed by the lungs (10%–15%). They can also reach other organs such as the kidney, brain, heart, bones, muscle, among others, although these locations do not exceed 10% of the detected cases (**Figure 1**)^(4,6).

The incubation time in man is several years and can be greater than 40 years. The disease symptoms include cyst expansion, pressure on adjacent structures, infection, rupture, and dissemination of cystic content in neighboring body cavities. When they rupture, spontaneously or secondarily to trauma or surgery, they can cause a seeding that will form multiple cysts (multiple secondary hydatidosis 20%–40%), secondary bacterial infections, anaphylactic reactions, among others^(4,5).

PRESENTATION OF THE CASE

A 21-year-old male patient from a rural area. He reaches the emergency department reporting a 2-year picture of

diffuse abdominal pain described as dull, ill-defined, and predominant in the left hypochondrium. The pain is occasionally associated with febrile episodes and nausea, which sometimes reaches emesis of dietary and biliary characteristics. The patient refers to periods of partial remission of the symptoms.

An important event in his history, which is related to the length of time symptoms are present, is a 14-month appendectomy prior to admission with subsequent drainage of the abdominal abscess. It required management by laparotomy.

When admitted to the emergency room, he was hemodynamically stable. On abdominal physical examination, pain on deep palpation in the left epigastrium and hypochondrium was found, with a mass sensation during palpation at this level. Paraclinicals of mild hyperbilirubinemia are taken at the expense of direct, mild leukocytosis and positive C-reactive protein (CRP), hypoalbuminemia, hydroelectrolyte disorder, given by hypopotassemia and hypochloremia, and normal tumor markers (**Table 1**).

A simple and contrasted abdominal and pelvic tomography was performed. Mild hepatosplenomegaly, simple

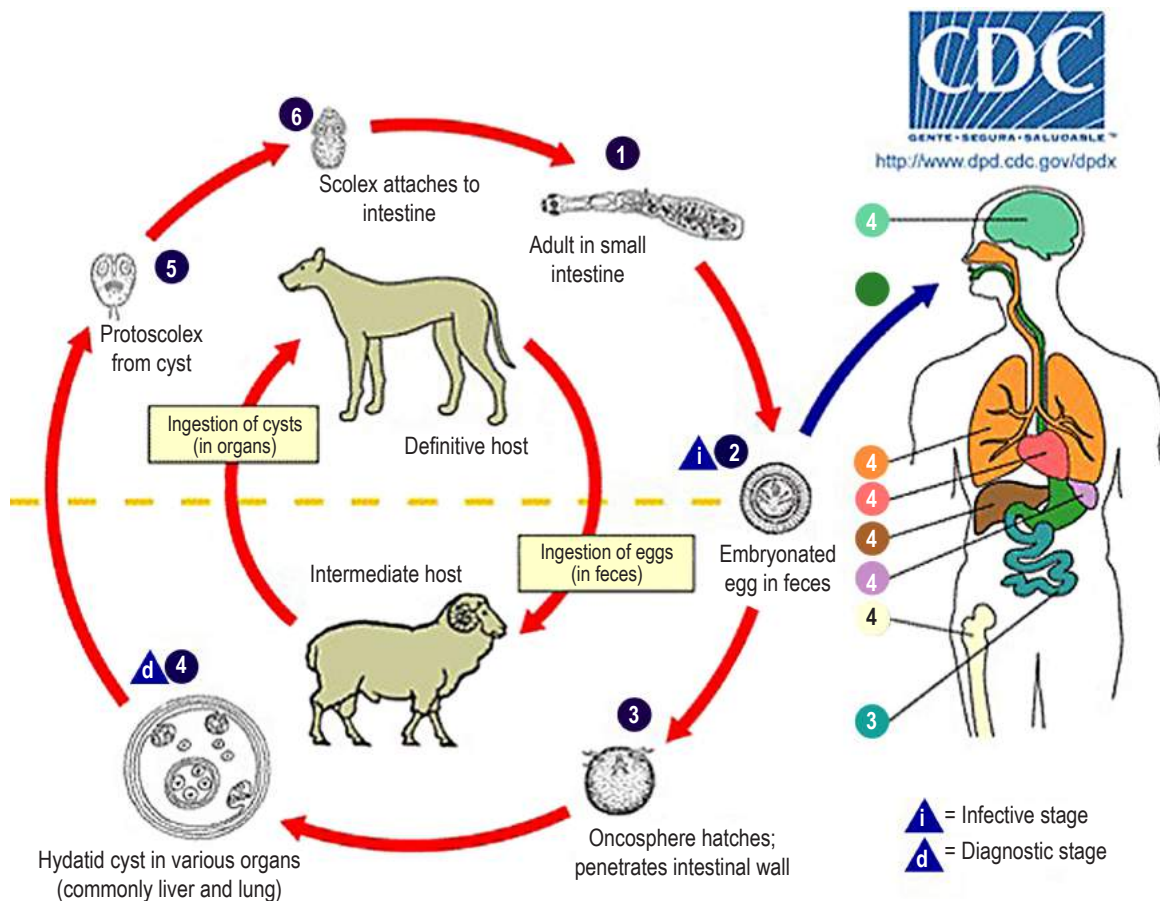


Figure 1. The life cycle of hydatidosis. Source: Courtesy of Centers for Disease Control and Prevention Image Library.

diffuse-distribution intrahepatic and splenic cysts, mesenteric cysts (also in diffuse form), and dilation of intestinal loops with significant distension of the duodenum (**Figure 2**) were documented. The results were evaluated by the General Surgery surgical board. Due to findings in imaging studies, it was considered that with unclear etiology, residual collections of previous surgical procedures should be discarded. Exploratory laparotomy should be taken, with cysts resection performed and a pathological study to define the etiology and final behavior.

Table 1. Admission laboratory tests

Paraclinical	Report
Complete blood count	Leukocytes 14,4; neutrophils 73.4%; lymphocytes 12.5 %; hemoglobin 13.3; hematocrit 42,6; platelets 290
Hepatic profile	Direct bilirubin 0.57; total bilirubin 1.03; indirect bilirubin 0.46; GOT 16; TGP 16.6; alkaline phosphatase 93
Electrolytes	Ionized calcium 1,1; sodium 141,6; potassium 2,95; chlorine 97,1
Renal function	Ureic nitrogen 7,4; creatinine 0.62
Nutritional Profile	Total proteins 7; albumin 2,7
Tumor Markers	CA 19-9:3 (negative); alpha-fetoprotein 0.5 (negative); carcinoembryonic antigen 0.5 (negative)
Others	PCR 28,3

During the surgical procedure, peritoneal fluid of a moderate amount is appreciated. Multiple peritoneal lesions of cystic appearance: 2 to 3 cm, those of smaller size, and up to 7 cm, the largest. The liquid is located at the root of the mesentery, and it displaces the ascending colon and duodenum, which explains the alimentary emesis episodes (**Figure 3**).

FOLLOW-UP AND RESULTS

The pathology report of these lesions corresponded to hydatid cystic lesions (echinococcosis), with macroscopic documentation (**Figure 4**) and microscopy study by H&E stain, where numerous scolex are seen inside the cystic cavity (**Figure 5**). The patient presented good clinical evolution after surgery. In-hospital treatment with albendazole 400 mg every 12 hours is initiated for 3-month cycles until 3 cycles are completed with laboratory controls using blood, tomographic and clinical counts every 3 months. The patient is in periodic check-ups with good clinical evolution.

DISCUSSION

The diagnosis of *E. Granulosus* infection is based primarily on clinical findings, serology, and imaging techniques. At least one of the following clinical diagnostic criteria must be met: anaphylactic reaction due to cyst rupture; symptomatic cystic mass, diagnosed by imaging techniques; incidentally diagnosed cyst by imaging techniques in an asymptomatic patient. The established diagnosis is determined by the characteristic lesion diagnosed by imaging

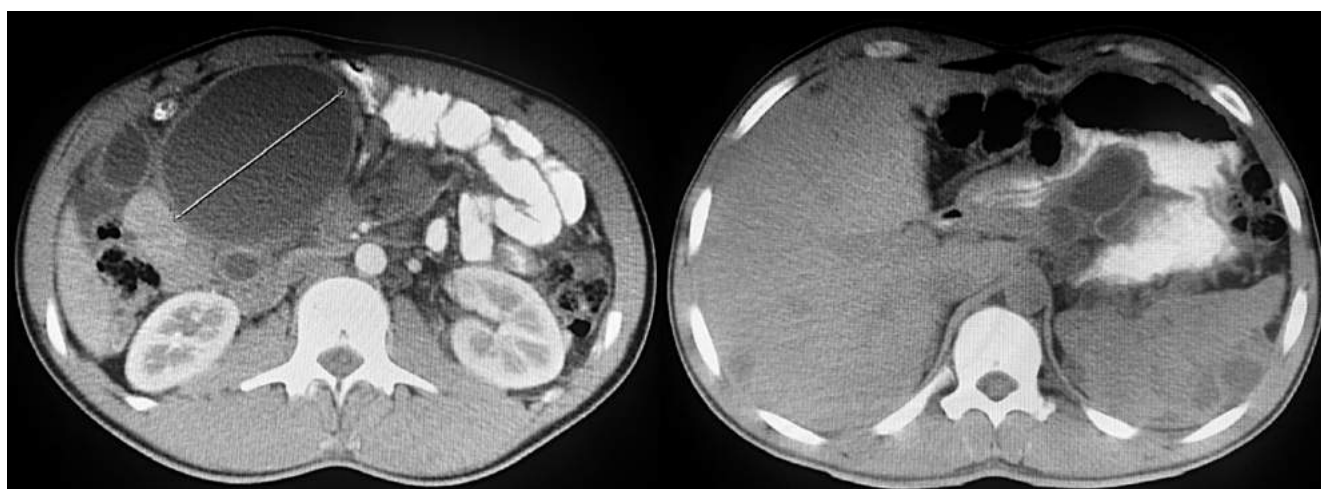


Figure 2. Simple and contrasted abdominal and pelvic tomography. Axial section showing numerous rounded lesions of liquid content, encapsulated and distributed at the root of the mesentery, liver, spleen, and peritoneum.

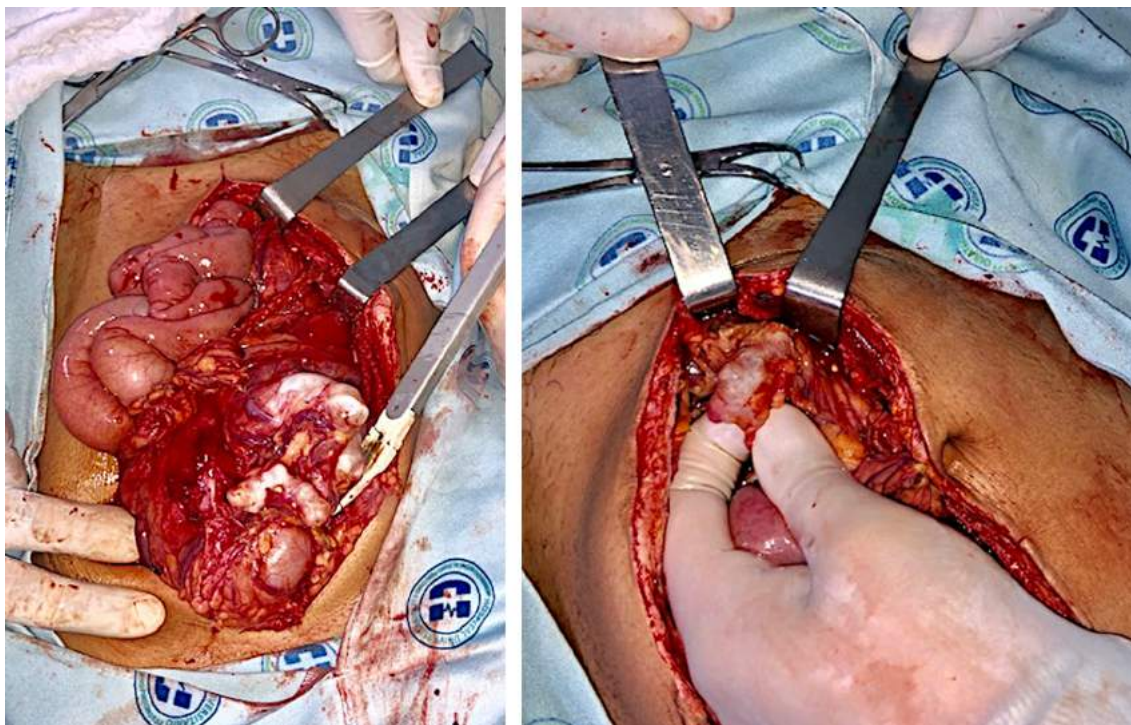


Figure 3. Intraoperative findings. Multiple cystic-like lesions in the peritoneum and root of the mesentery.



Figure 4. Macroscopic findings. Cystic-like lesions of whitish cover.

techniques, a positive serology, microscopic examination of the fluid or consistent histological sample, and macroscopically compatible surgical findings⁽³⁾.

In the presented clinical case, what was previously described, is verified. The patient met the second clinical judgment, and

the diagnosis was verified through images, surgical findings, and macro and microscopic studies. It was considered that the peritoneal dissemination was due to the reoperation of the appendectomy complication (abscess), which ruptured one of the cysts with the manifest consequence in this clinical case.

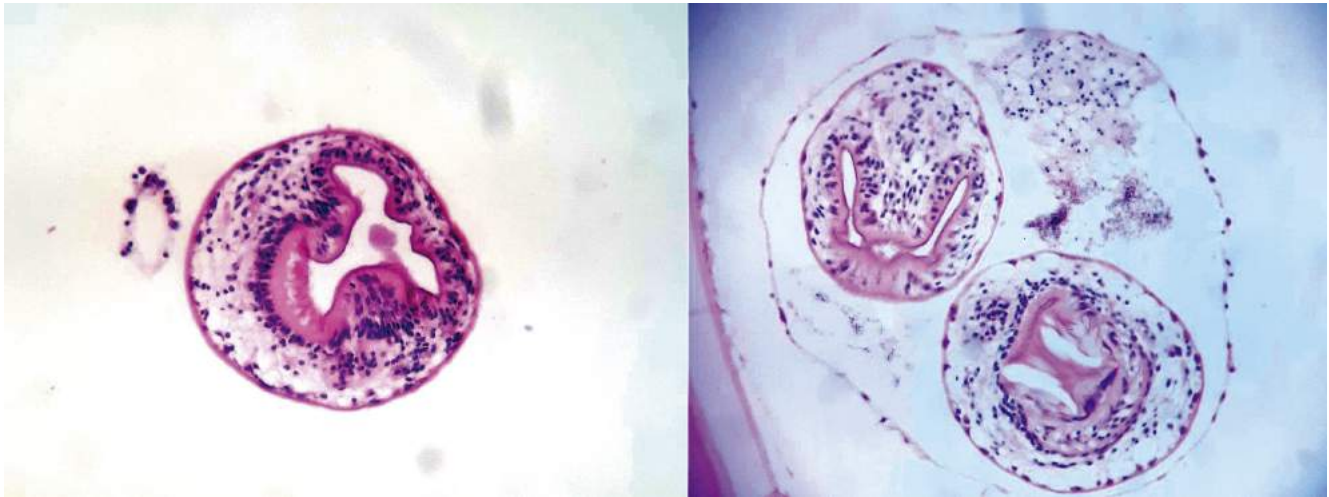


Figure 5. Microscopic findings. Cystic lesions with images inside, corresponding to scolex.

There are different imaging techniques for the diagnosis. The abdominal ultrasound is the chosen one in abdominal cystic lesions⁽³⁾, using the World Health Organization and International Working Group (WHO/IWG) classification⁽⁷⁾. This classification evaluates the activity of hydatid cystic lesions according to the activity and number of loculi. In this way, the response to chemotherapeutic treatment can be assessed to compare different types of management and evaluate their response⁽⁸⁾. The first clinical group corresponds to the types of cysts EC 1 and 2. These cysts indicate that they are active for their fertility, with viable protoscolex. The second group is EC type 3, which are cystic lesions in a transitional stage where the host's response to treatment has compromised the cyst integrity. The third clinical group comprises CE types 4 and 5, inactive cysts that normally lose their fertility and are the final degenerative status⁽⁸⁾. Computed tomography and magnetic resonance imaging are techniques of choice in subdiaphragmatic and multiple lesions, in the presence of complicated cysts with fistulas or abscesses, extra-abdominal localization cysts, and as a form of presurgical assessment^(3,9).

Currently, there is no unification of criteria regarding the best treatment of cystic echinococcosis, not even in relation to the need to treat or not the infection. The treatment is based on three fundamental pillars:

- The use of antiparasitics is mandatory in all patients.
- Procedures for interventional purposes should be preferred over palliative surgery whenever possible.
- Radical surgery is the first option in all susceptible cases to total resection of lesions. This should always be based on the clinical condition and characteristics of the cysts^(3,7).

Different techniques for the curative treatment of hydatid cysts have been described: percutaneous needle aspiration, hypertonic saline injection, content reaspiration, resection of the protruding dome with aspiration-exeresis of its content, cystoperichistectomy and hepatic resection⁽¹⁰⁾. In general, surgeons from non-endemic areas prefer radical techniques, while those from endemic areas use more conservative techniques⁽¹⁰⁾. In the case of symptomatic patients or with complicated hydatid cysts (abscess, abdominal cavity rupture, opening to the bile duct, thoracoabdominal transit), the treatment of choice should be surgery, either conventional or laparoscopic. Preoperative chemoprophylaxis with 10 mg/kg/day of albendazole is suggested for at least 15 days. Albendazole can still be used in all cases for 3 cycles in the postoperative period^(11,12).

The mean postoperative mortality is 2.2%, approximately 6.5% of recurrent cases after an intervention, leading to prolonged recovery periods⁽²⁾. In our case, the diagnosis was made during the intraoperative period. Radical resection of most cysts was carried out, given the complexity of this pathology, due to its multiple dissemination at the level of organs and the peritoneal cavity.

Regardless of the performed treatment, the patients' follow-up with this pathology is especially important. Revisions are carried out during the first 2 years on a semi-annual basis, with control imaging tests and serological determination. It is recommended to continue follow-up for long periods. Recurrences of the disease are documented up to 10 years after apparently successful treatment has been applied⁽³⁾. The outcome of infection varies depending on the stage of the disease. Approximately

15% of patients are taken to surgery after 10 to 12 years of the initial diagnosis. 75% of these patients may remain asymptomatic.

CONCLUSION

Disseminated abdominal echinococcosis, although it is a rare pathology in our environment and the world literature,

should always be suspected when clinical, imaging, and serological findings suggest it. It is important to identify this pathology to initiate timely medical management and subsequent surgical treatment for total resection of cystic lesions, if technically possible. Finally, the patient must remain in a strict follow-up and control to eradicate the disease adequately by means of medical treatment in prolonged cycles with albendazole.

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History and Gastroenterology. Crohn's disease

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Burrill Bernard Crohn was born in New York on June 13, 1884, and died on July 29, 1983, at 99 (**Figure 1**)⁽¹⁾. He was the son of a German-Jewish immigrant family who arrived in New York at the end of the 19th century⁽¹⁾. At age 13, Burrill entered the City University of New York, graduating at age 18. In 1911, he earned his medical degree from Columbia University⁽¹⁾. He then entered Mount Sinai Hospital for a 2-year training program. Emanuel Libman was his mentor⁽¹⁻³⁾.



Figure 1. Burrill B Crohn. Taken from Wikipedia.

Crohn joined the hospital first as an intern in the Pathology department (chosen from 120 candidates) and then as an assistant. Later, he worked in the Chemical Physiology department, studying the pancreas function⁽³⁾.

In 1920, at the age of 36, Crohn was the head of the gastroenterology service at Mount Sinai Hospital. He was appointed president of the American Gastroenterological Association in 1935^(1,3,4). In 1932 he presented a paper with Ginzburg and Oppenheimer originally called “terminal ileitis,” then changed it to “regional ileitis,” following the advice of Bargen from the Mayo Clinic⁽²⁾.

HISTORY

The Italian physician Morgagni made the first description of Crohn's disease from a young patient autopsy with diarrhea and weakness in 1769^(5,6). In 1813, two London sur-

geons, Combe and Saunders, reported the case of a patient who had thick ileal walls, ulcers in the cecum, and ascending colon. In 1913, Dalziel, a Scottish surgeon unknown to doctors at Mount Sinai Hospital, published a series about 9 patients who possibly had Crohn's disease^(2,6) in the British Medical Journal.

While Crohn was studying the pancreas and its exocrine secretions, surgeon Berg performed the first successful subtotal gastrectomy to treat ulcerative disease^(3,7). Two young surgeons, Ginzburg (1898–1988) and Oppenheimer (1900–1974) worked for some years on the diagnosis, treatment, and data collection of patients operated by Berg. They had intestinal obstructions, especially in the ileocecal region. When examining the resected areas, they were struck by the characteristic inflammation of these lesions, the intestinal walls thickness, and the absence of germs (especially tuberculosis), which could explain the clinical picture of the operated patients^(6,7).

According to Ginzburg, in 1931, after reviewing the anatomopathological studies of two patients operated by Berg, Crohn found that the latter's team was collecting data on this type of ileitis. Crohn spoke with Berg to include him as an author in the publication of an article on the so-called "terminal ileitis." Berg, who had already operated on 12 patients with these characteristics, declined the invitation because he did not participate in the article's writing (he did not consider it ethical to appear as an author) but suggested that he request Ginzburg's patient files⁽⁷⁾. Thus, all 14 patients in the original study were completed.

In May 1932, Crohn presented the manuscript at the American Medical Association (AMA) annual meeting. Neither Ginzburg nor Oppenheimer was mentioned at that time. This led Ginzburg to request a departmental meeting chaired by Berg. After hearing the parties involved, the committee that reviewed the case decided that Ginzburg and Oppenheimer⁽⁷⁾ should be placed as authors of the article in addition to Crohn.

The article was finally published in the Journal of the American Medical Association (JAMA) in October 1932

and was twice as extensive as the original manuscript⁽⁸⁾. Crohn added this new information from his experiences and clinical observations. JAMA published the manuscript and put the authors' names in alphabetical order, according to the custom of that time. This is why the eponym began to be forged in the minds of the article's readers. Finally, in 1939, Armitage and Wilson proposed that it be called Crohn's disease to simplify and unify the description of the disease and pay a well-deserved tribute to Crohn⁽⁷⁾.

If Berg had agreed to be part of the original article, we would be talking about Berg's disease (as JAMA published in alphabetical order, Berg would have been the first author). The truth is that the eponym was assigned seven years later, not only based on the article. Crohn became a specialist in inflammatory intestinal diseases and gave lectures on the subject worldwide^(3,7). In addition, he accepted the critics and suggestions. An example of this is that during his presentations, Bagen, from the Mayo Clinic, suggested changing the term "terminal ileitis" to "regional ileitis" since all the patients were alive and in good condition. He found it suitable and changed the disease's name^(6,7).

Crohn clearly described the disease and insisted that his name not be used as the eponym of this disease⁽⁴⁾. He finally gave up on this proposal. Crohn was a modest physician, devoted to the study and treatment of inflammatory bowel diseases, universally admired, and well-deserving of recognition as a true teacher^(1,3). He received numerous recognitions during his life.

Some of his hobbies were gardening, painting (watercolor), and a particular interest in the American Civil War⁽³⁾. Crohn was a great admirer of Abraham Lincoln. When President Eisenhower suffered from ileitis in 1956, he tried to assure the people that the president would recover without difficulty⁽⁴⁾.

His career is immortalized in the Burrill B. Crohn Research Foundation, based at the Mount Sinai Hospital⁽¹⁾. In 1960, thanks to the publication of Lockhart-Mummery and Morson, the concept that Crohn's disease could affect any area of the digestive system was generalized⁽⁵⁾.

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