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**TESI DI LAUREA**

## **TIMING OF ILEOCOLONIC ANASTOMOSIS IN ILEOCECAL RESECTION IN CROHN'S DISEASE**

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## ABSTRACT

**Background** - Crohn's disease (CD) is a chronic inflammatory disorder affecting the gastrointestinal tract with no current curative treatment. Despite significant improvements in medical treatments, surgery is still necessary in most cases, especially in the management of complications. Intestinal resection of the terminal ileum followed by ileocolonic anastomosis is the most performed surgery for Crohn's disease since it typically affects the terminal ileum. Among different types of anastomoses, the side-to-side anastomosis is currently recommended by European Crohn's and Colitis Organisation (ECCO) guidelines, and the laparoscopic method appears to be preferred. However, it remains uncertain whether performing the anastomosis intracorporeally or extracorporeally ultimately affects postoperative outcomes, leaving the decision up to the surgeon. Currently, there are no studies in the literature comparing these outcomes in ileocolic anastomoses.

Therefore, our study aims to investigate any differences between the two anastomosis types in terms of disease activity, body image, quality of life, operating time, and clinical and surgical recurrence-free survival time.

**Methods** - We performed a retrospective analysis of 50 consecutive patients who underwent ileocecal resection followed by ileocolonic side-to-side anastomosis in our department from 2020 to 2023. For each patient, surgical records, discharge letters, and outpatient follow-up visits were thoroughly analyzed. In July 2023, 48 patients agreed to participate in a telephone interview to assess patients' clinical disease activity (Harvey-Bradshaw), quality of life (Cleveland Global Quality of Life), and body image (Body Image Questionnaire) after surgery.

**Results** - 16 and 34 patients underwent intracorporeal and extracorporeal anastomosis, respectively. The disease activity (Harvey-Bradshaw Index) did not show significant differences in single item or total HBI scores between the two groups. However, patients with extracorporeal anastomosis had slightly higher scores for item HB3 (number of liquid/soft stools per day) ( $p = 0.0778$ ), moreover patients with extracorporeal anastomosis had a slightly higher HB total score ( $p = 0.0580$ ).

The Body Image Questionnaire (BIQ) results indicated that patients who underwent intracorporeal anastomosis were more satisfied with their bodies (BIQ1,  $p = 0.0270$ ), felt more attractive (BIQ3,  $p = 0.0570$ ), and felt more masculine/feminine (BIQ4,  $p = 0.0814$ ) compared to those with extracorporeal anastomosis although only the first item showed a statistical significance. We performed additional analysis of the results, specifically excluding patients who underwent open surgery. The previously slight differences were no longer observed, except for item BIQ1 ( $p = 0,0257$ ). No differences were found in quality of life, health, energy level, or postoperative complications between the two groups. However, in terms of operating time, intracorporeal anastomoses showed a slightly shorter operating time, although this did not reach statistical significance. On the other hand, intracorporeal anastomoses appear to be associated with a slight, though not statistically significant, tendency to recur.

**Conclusions** - Our study suggests that intracorporeal anastomosis seems to have slightly functional and aesthetic advantages compared to extracorporeal anastomosis, although these findings did not reach statistical significance. In addition, intracorporeal anastomosis appears to be faster to perform, but it seems to be associated with a higher likelihood of disease recurrence. In terms of postoperative quality of life, no significant differences were observed between the two types of anastomoses, and there were no significant differences in postoperative complications. It's important to note that these results are based on a limited sample size and follow-up period, and further studies are needed for confirmation.

**Keywords** - Crohn's disease, ileocolonic anastomosis, intracorporeal anastomosis, extracorporeal anastomosis, quality of life, body image, disease activity, operatory time, disease recurrence.

## RIASSUNTO

**Introduzione e scopo** - La malattia di Crohn (CD) è una patologia infiammatoria cronica che colpisce il tratto gastrointestinale per la quale attualmente non vi è alcun trattamento curativo. Nonostante i significativi progressi dei trattamenti medici, l'intervento chirurgico detiene ancora un ruolo fondamentale nella maggior parte dei casi, soprattutto per la gestione delle complicanze. La resezione intestinale dell'ileo terminale seguita da un'anastomosi ileocolica è l'intervento chirurgico più eseguito per la malattia di Crohn, dal momento che questa colpisce tipicamente l'ileo terminale. Tra i diversi tipi di anastomosi, quella latero-laterale è attualmente raccomandata dalle linee guida dell'European Crohn's and Colitis Organization (ECCO) e il metodo laparoscopico sembra essere preferito. Tuttavia, rimane incerto se l'esecuzione dell'anastomosi per via intracorporea o extracorporea influisca in ultima analisi sui risultati post-operatori, lasciando la decisione nelle mani del chirurgo. Attualmente non esistono studi in letteratura che confrontino questi risultati nelle anastomosi ileocoliche. Pertanto, il nostro studio si propone di indagare le eventuali differenze tra i due tipi di intervento in termini di attività di malattia, immagine corporea, qualità di vita, tempi operatori e tempi di sopravvivenza clinica e chirurgica libera da recidive.

**Metodi** - Abbiamo eseguito un'analisi retrospettiva di 50 pazienti consecutivi sottoposti a resezione ileocecale seguita da anastomosi ileocolica latero-laterale nel nostro reparto dal 2020 al 2023. Per ogni paziente sono state analizzate a fondo le cartelle cliniche, le lettere di dimissione e le visite ambulatoriali di controllo. Nel luglio 2023, 48 pazienti hanno accettato di partecipare a un'intervista telefonica con l'obiettivo di valutare l'attività clinica della malattia (Harvey-Bradshaw), la qualità della vita (Cleveland Global Quality of Life) e l'immagine corporea (Body Image Questionnaire) dei pazienti stessi dopo l'intervento.

**Risultati** - 16 e 34 pazienti sono stati sottoposti rispettivamente ad anastomosi intracorporea ed extracorporea. L'attività della malattia (indice di Harvey-Bradshaw, HBI) non ha mostrato differenze significative nei punteggi dei singoli items o del totale dell'HBI tra i due gruppi.

Tuttavia, i pazienti con anastomosi extracorporea avevano punteggi leggermente più alti per l'item HB3 (numero di feci liquide/morbide al giorno) ( $p = 0,0778$ ); inoltre, i pazienti con anastomosi extracorporea avevano un punteggio totale dell'HBI leggermente più alto ( $p = 0,0580$ ). I risultati del Body Image Questionnaire (BIQ) hanno indicato che i pazienti sottoposti ad anastomosi intracorporea erano più soddisfatti del proprio corpo (BIQ1,  $p = 0,0270$ ), si sentivano più attraenti (BIQ3,  $p = 0,0570$ ) e si sentivano più maschilini/femminili (BIQ4,  $p = 0,0814$ ) rispetto a quelli sottoposti ad anastomosi extracorporea, sebbene solo il primo item abbia mostrato una significatività statistica. Non sono state riscontrate differenze nella qualità della vita, nella salute, nel livello di energia o nelle complicanze postoperatorie tra i due gruppi. Tuttavia, le anastomosi intracorporee hanno mostrato un tempo operatorio necessario per la loro esecuzione leggermente inferiore, anche se questo dato non ha raggiunto la significatività statistica. In ultima analisi, le anastomosi intracorporee sembrano avere una leggera tendenza, pur non statisticamente significativa, alla recidiva di malattia.

**Conclusioni** - Il nostro studio suggerisce che l'anastomosi intracorporea possa presentare lievi vantaggi funzionali ed estetici rispetto all'anastomosi extracorporea, sebbene questi risultati non abbiano raggiunto la significatività statistica. Inoltre, l'anastomosi intracorporea sembra essere più veloce da eseguire, ma sembra essere associata a una maggiore probabilità di recidiva della malattia. In termini di qualità di vita post-operatoria, non sono state osservate differenze significative tra i due tipi di anastomosi e non ci sono state differenze significative nelle complicazioni post-operatorie. È importante notare che questi risultati si basano su una numerosità limitata del campione e su un breve periodo di follow-up; pertanto, sono necessari ulteriori studi per una conferma definitiva.

**Parole chiave** - Malattia di Crohn, anastomosi ileocolica, anastomosi intracorporea, anastomosi extracorporea, qualità di vita, immagine corporea, attività di malattia, tempo operatorio, recidiva di malattia.



## **1. INTRODUCTION**

### **1.1 BACKGROUND**

Crohn's disease (CD) is a chronic inflammatory disorder affecting the gastrointestinal tract. It belongs to the spectrum of chronic idiopathic inflammatory bowel disease (IBD) along with ulcerative colitis (1). It can cause lesions from the mouth to the anus, leading to extraintestinal complications (2). The terminal ileum and colon are the most common areas affected, although any segment of the gastrointestinal tract may be impacted. The inflammation is typically transmural, asymmetrical, and segmental (3). Patients with CD experience periods of flares and remissions during their disease course (4). Common presenting symptoms include abdominal pain, fever, weight loss, fatigue, and clinical signs of bowel obstruction or diarrhea with passage of blood or mucus (2,5). Although the exact cause is unknown, it is believed that the onset of CD can be triggered by the interplay of factors including genetic predisposition, environmental factors, microbiota dysbiosis, and defects in innate immunity and intestinal barrier function (6).

CD treatment is multidisciplinary and aims to control inflammation and induce clinical remission. Depending on the severity of the disease, it may involve pharmacologic therapy, biologics, immunomodulators, or surgery, which plays a crucial role in treating complications such as stenosis, perforations, fistulas, and abscesses (4,6). Due to the rising global prevalence of CD in adults and children, an increasingly diverse group of clinicians is now involved in its treatment (5,6).

### **1.2 EPIDEMIOLOGY**

Crohn's disease, together with ulcerative colitis, is the most prevalent type of inflammatory bowel disease (7,8). Throughout the latter half of the 20th century, there was a steady increase in CD incidence observed in Northern Europe and North America. This resulted in the classification of the disease as a typical condition of industrialized nations. However, although it remains more prevalent in urban and developed regions, the disease is currently spreading rapidly in Asian countries that are undergoing rapid urbanization (1,3,9,10).

The countries with the highest annual incidence are Australia (29.3/100,000 population), Canada (20.2/100,000), New Zealand (16.5/100,000), and Northern Europe (10.6/100,000); those with the highest prevalence are Europe (322/100,000), Canada (319/100,000) and the USA (214/100,000) (9).

Increased prevalence is associated with the Caucasian race and higher education level (2). The onset of Crohn's disease typically occurs between the second and fourth decades of life, with a second, smaller peak occurring between the ages of 50 and 60 (3). There is no gender difference in the prevalence of Crohn's disease in adults; however, individuals of Ashkenazi Jewish descent have a higher incidence of the disease (10).

Surprisingly, regions that historically had low rates of inflammatory bowel disease (IBD) are experiencing a notable increase in its occurrence, which corresponds to their progress in development. Specifically, areas of Asia, where certain countries are rapidly urbanizing, are experiencing a significant increase in the annual incidence of Crohn's disease. Rates have reached 0.54 cases per 100,000 people. In addition, studies of migrants have shown that those who move from low-prevalence areas to high-prevalence areas have an increased risk of developing Crohn's disease and that this risk is further increased in the offspring of migrants, suggesting that environmental factors and early life exposures have a significant impact on the development of this disease (3,11).

### **1.3 ETIOPATHOGENESIS**

Crohn's disease is believed to be the result of a complex interplay between genetic susceptibility, environmental factors, and the composition of the gut microbiota. This complex relationship ultimately results in an abnormal immune response in the mucosa and impaired function of the epithelial barrier (3).

#### **1.3.1 Genetic susceptibility**

Genetics plays an important role in determining susceptibility to IBD. (12). Approximately 15% of patients with Crohn's disease report a family history of the condition, while a smaller percentage report a family history of ulcerative colitis.

First-degree relatives of individuals with Crohn's disease have a relative risk of developing inflammatory bowel disease of about 5% in non-Jewish populations, and 8% in Jewish populations. When both parents are affected, the estimated risk for their offspring to develop the disease is one in three. The rates of concordance for the development of CD in monozygotic twins can vary between 20% and 50%, whereas the rates for dizygotic twins are approximately 10%. These figures indicate a noteworthy genetic predisposition but not an absolute one. Even among twins, there can be variations in the type of IBD and the natural course of the disease, which are influenced by environmental factors, such as smoking, as well as other individual factors (10).

Scientists have identified at least 70 chromosomal loci associated with the development of CD through genome-wide association studies (GWAS) and meta-analyses (7). The first GWAS was performed in 2005 in a Japanese population, identifying TNFSF 15 as a risk locus. This led to numerous subsequent studies, during which the genes and pathways identified, have provided a wealth of information about the underlying biological mechanisms of Crohn's disease.

The most important gene known to influence CD susceptibility is NOD2 (13). Within the NOD2/CARD15 gene, three distinct mutations have been recently linked to CD: two missense mutations (Arg702Trp and Gly908Arg) and one frameshift mutation (3020insC) (14). These play an integral part in microbial identification and detection (13). Experimental evidence links them to a weakened inflammatory cytokine response to muramyl dipeptide and ineffective autophagy, as well as to the transcription of IL10 (5). Patients with heterozygous NOD2/CARD15 polymorphisms have a 2-4 times increased risk of developing CD, while those with homozygous alleles have a 20-40 times increased risk (7,10).

A meta-analysis of 36 studies found that any presence of a mutant NOD2 allele was associated with complicated disease (13) along with ileal involvement, earlier age of onset, and a family history of CD (10). This finding has not been corroborated by other European studies, which only found an increased likelihood of surgery (7).

GWAS analyses revealed the involvement of two more major genes, ATG16L1 and IRGM, in the pathogenesis of CD (11). Additionally, other genes associated with both the innate (TLR4, CARD9, IL23R, STAT3) and adaptive immune systems (HLA, TNFSF15, IRF5, PTPN22) were also implicated (15).

Latest GWAS have shown that over 50% of IBD susceptibility genetic markers are shared with other immune-mediated diseases, including ankylosing spondylitis, psoriasis, primary immunodeficiency, and mycobacterial diseases (16). Extraintestinal manifestations are more frequently observed in CD patients with HLA-A2, HLA-DR1, and HLA-DQw5. These manifestations are also more common among carriers of the PTPN22 variant, which increases the risk almost two-fold (13).

In conclusion, although improved statistical models and larger sample sizes may lead to the identification of more susceptibility loci in the future, this trait currently contributes only slightly more than 20% to the heritability of Crohn's disease, underscoring the importance of epigenetic and environmental factors (5).

### **1.3.2 Environmental factors**

#### *Smoking*

Cigarette smoking has been extensively studied as an environmental risk factor for inflammatory bowel disease. In the case of Crohn's disease (CD), smoking is associated with increased risk, as shown in the Mahid et Al. meta-analysis, whereas in ulcerative colitis (UC) current smoking appears protective (17). The possible link between the impact of smoking and the development of CD may stem from its impact on the gut microbiome; CD patients with smoking have a dysbiosis of the gut microbiome (15).

Smoking has also been associated with earlier development of CD, more frequent use of immunosuppressants, more surgical interventions, and more postoperative relapse (10).

#### *Diet*

Observational studies have shown a negative association between dietary fiber intake and CD susceptibility. In the Nurses' Health Study, prolonged intake of dietary fiber was associated with a reduced risk of CD (OR 0.59, 95% CI 0.39-0.90) (10). The positive impact of dietary fiber is particularly significant when obtained from fruits. This effect could be attributed to multiple mechanisms. First, the fiber in fruits can be broken down into short-chain fatty acids that can suppress inflammatory mediators and NF- $\kappa$ B.

Additionally, they may inhibit the translocation of mucosa-associated adherent and invasive *E. coli*, which is increased in individuals with CD.

Certain components of cruciferous vegetables, such as indole-3-carbinol (I3C), activate the aryl hydrocarbon receptor (AhR) present in intestinal intraepithelial lymphocytes, thereby safeguarding against environmental antigens by binding to sequences in the nucleus. Mice who lack AhR are more vulnerable to colitis and exhibit different patterns of gut bacterial colonization (19).

#### *Exposure in early life and other risk factors*

Several hypotheses suggest that early-life exposures, from prenatal stages to age 5, play a role in the development of inflammatory bowel disease.

A Canadian meta-analysis examining the impact of childhood hygiene and living conditions on the development of IBD found that growing up in rural areas, with siblings and farm animals nearby, may offer protection against IBD, particularly CD. Urban upbringing may limit early exposure to infections, which may reduce microbiota diversity and promote a pro-inflammatory immune response (20,21).

A meta-analysis by Agrawal et al. found that exposure to antibiotics, passive tobacco smoke, and a diagnosis of otitis media during early life may lead to CD (20,22). Conversely, extended periods of breastfeeding seem to be a protective factor (23). Some studies have indicated a potential correlation with contraceptives (24) and NSAID use (25). Following infectious gastroenteritis, there is an elevated risk of developing CD within the subsequent year, although the overall risk remains low (26).

A further meta-analysis showed a higher incidence of CD, particularly in the year following appendectomy, with a subsequent decrease in the following years. This connection could be due to the difficulties in diagnosing early Crohn's disease in patients, where acute appendicitis serves as the first indication of Crohn's disease (5,25).

### **1.3.3 Immune system and intestinal barrier**

The pathogenesis that appears to underlie the onset of Crohn's disease is essentially a dysfunction of the intestinal barrier and a massive disruption of the immune response, both innate and adaptive.

Several abnormalities causing intestinal barrier dysfunction have been identified in patients with CD. For example, inadequate mucin coverage due to decreased MUC1 gene expression was found in the inflamed terminal ileum of Crohn's patients.

Several genome-wide association studies have linked Crohn's disease to the MUC1, MUC19, and PTGER4 genes.

In addition, alterations in the expression of tight junction proteins such as claudins result in junctional loosening and subsequent increased permeability. This allows luminal antigens to reach the lamina propria which is rich in immune cells.

Paneth cells of CD patients with the specific variant of the autophagy gene ATG16L have reduced levels of antibacterial peptide granules such as alpha-defensins. Furthermore, research has found correlations between XBP1 and NOD2 polymorphisms and Paneth cell dysfunction. Endoplasmic reticulum stress may also impair the response to unfolded proteins in goblet and Paneth cells, leading to inflammation (5).

The development of Crohn's disease is also significantly impacted by microbial sensing. Microbial patterns such as lipopolysaccharide, muramyl dipeptide, RNA, and dietary components trigger innate immune cells through receptors such as TLR and NLR in the intestinal mucosa. Dendritic cells, with the broadest array of receptors, direct immune responses, and tolerance. They sample luminal antigens through transepithelial dendrites. In Crohn's disease, dendritic cell distribution and phenotype are related to disease activity, with increased TLR2, TLR4, and lipopolysaccharide responses reported (5).

Crohn's disease is also characterized by the activation of T lymphocytes and macrophages, with a predominant cell-mediated immune response associated with the activity and release of mediators by Th-1 and Th-17 lymphocytes. Increased levels of INF- $\gamma$ , IL-12, IL-18, IL-21, and TNF- $\alpha$  are found in the intestinal mucosa, capable of maintaining and perpetuating the inflammatory process (25).

### *Microbiota*

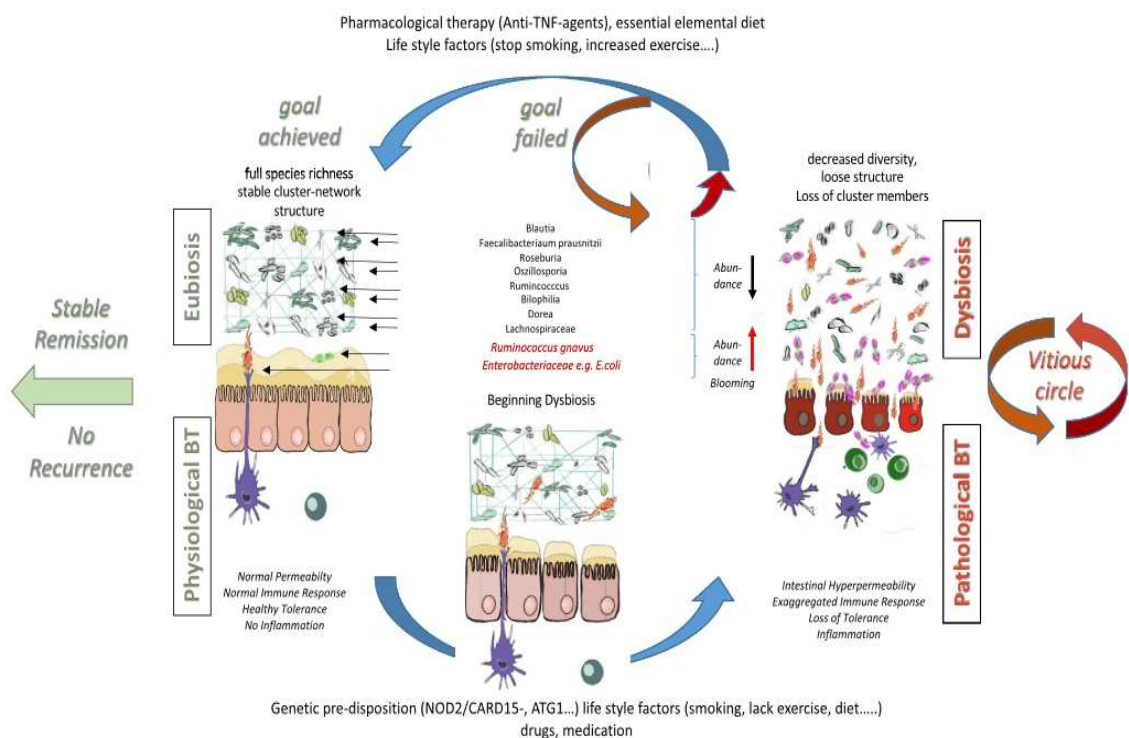
The colonization and development of the gut microbiota are influenced by various factors, such as the host's immune and epithelial responses, environmental exposures like diet and antibiotics, and potentially genetic factors such as NOD2.

In turn, the microbiota has a significant impact on the host's epithelial and immune functions through its structural components and metabolic activity. This influence may lead to a susceptibility to IBD at an early stage of life (27).

Metagenomic studies have shown that the human gut is colonized by four primary bacterial phyla: Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria, which include several anaerobic bacteria. Individuals diagnosed with CU and CD exhibit altered microbiota indicating a state of dysbiosis, characterized by reduced diversity, particularly in Firmicutes and Bacteroidetes, and elevated Gamma-proteobacteria and Actinobacteria levels in comparison to healthy individuals (5,12) Moreover, a decrease in *Faecalibacterium prausnitzii*, a type of Firmicute with anti-inflammatory properties, has been linked to an increased risk of postoperative recurrence of ileal CD.

Additionally, roughly one-third of patients exhibit an increase in invasive adherent *E. coli*, which can cross the mucosal barrier, adhere to, and invade intestinal epithelial cells, and ultimately survive and replicate in macrophages. This results in the secretion of high levels of TNF- $\alpha$ . Finally, research suggests a relative expansion of certain viral (caudovirales) and fungal species in CD patients' microbiota (25).

It is worth noting that Crohn's disease is not solely attributed to reduced commensal diversity or dysbiosis but rather genetic susceptibility is necessary (5,25).



**Fig. 1** - Interaction of microbiome, intestinal barriers, and translocating bacteria in healthy conditions and active CD (12).

## 1.4 CLINICAL PRESENTATION

Crohn's disease exhibits a wide range of variation in its onset and clinical course, which is influenced by factors such as the location, extent, level of activity, and pattern of disease (25).

Abdominal pain and chronic diarrhea are commonly reported symptoms that need to be investigated, especially in younger patients (25). The pain is predominantly located in the mesogastrium and right iliac fossa. It varies in intensity and frequency; it may occur at night and does not subside after defecation. Rectorrhagia and tenesmus are associated with sigmoid colon and rectal lesions (25). Hematochezia and/or mucus in the stool may be seen in up to 40–50% of patients with CD, but less frequently than in ulcerative colitis (26).

Systemic symptoms such as uneasiness, anorexia, weight loss, or fever are also commonly encountered. Symptoms may be present for months or even years in many patients before diagnosis (28). Abdominal pain and weight loss are seen in about 80% and 60% of patients, respectively, before diagnosis (26).

Delayed growth and puberty are frequent occurrences in children (9). CD may present with a clinical picture similar to that of irritable bowel syndrome (IBS). Although IBS is more prevalent than Crohn's Disease (CD), any concurrent systemic symptoms, presence of blood in stools, or unexplained weight loss should warrant additional investigation (26).

The disease usually has a relapsing-remitting course, with periods of exacerbation and periods of remission. Despite its typical chronic course, in 10% of cases, the onset can be acute, mimicking appendicitis (25).

Approximately 30% of patients start with perianal disease which may precede the onset of intestinal symptoms by years (25). Patients with distal colonic or rectal involvement have a higher risk of perineal disease than those with isolated ileal disease. Perianal abscesses, fistulas, edematous skin tags, elephant skin tags with surrounding erythema, and patches of vitiligo mixed within dermal scarring are common manifestations of perianal Crohn's disease. It is a significant health concern affecting the patient; therefore, managing it is essential (29).

Extraintestinal symptoms, usually arthritic, dermatologic, or ocular (9) may be present at the time of the diagnosis, and can occur without significant abdominal symptoms (28).



### *Extraintestinal manifestation (EIMs)*

EIMs occur in 21-36% of patients with IBD throughout their disease history. These manifestations can affect nearly any organ or system and can be a significant challenge for physicians managing IBD patients (28,29).

The most common EIMs include inflammatory arthropathies, such as peripheral seronegative polyarticular arthritis (found in 15-20%) related to CD flares (30) (27,31) or axial arthritis, ranging from asymptomatic sacroiliitis to ankylosing spondylitis (31).

Skin problems, including Erythema Nodosum (2-20% of cases) and Pyoderma Gangrenosum (0.5-2% of cases), may arise, in addition to ocular complications such as episcleritis and uveitis. Anemia is also common (30).

Less common extraintestinal manifestations of the disease include primary sclerosing cholangitis, pancreatitis, several pulmonary disorders such as bronchitis or bronchiectasis, osteoporosis, and thromboembolic events (31). On the other hand, cholelithiasis and nephrolithiasis are prevalent in patients with ileal disease and are caused by bile salt malabsorption and extensive ileal resections (25). Researchers in Hungary found associations of typical EIMs with IBD subtypes such as primary sclerosing cholangitis with UC and pyoderma gangrenosum with CD. EIMs are more common in CD associated with colon involvement and occasionally preceding colonic symptoms (26,32)

Female gender and steroid dependency seem to be also associated with the risk of developing EIMs (33).

**Table 1** - Extraintestinal manifestations of Crohn's disease (34).

Sites	Extraintestinal manifestations
Musculoskeletal system	<ul style="list-style-type: none"><li>• Arthritis: colitic type, ankylosing spondylitis, isolated joint involvement</li><li>• Hypertrophic osteoarthropathy: clubbing, periostitis</li><li>• Miscellaneous manifestations: osteoporosis, aseptic necrosis, polymyositis</li></ul>
Dermatologic and oral systems	<ul style="list-style-type: none"><li>• Reactive lesions: erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizing vasculitis</li><li>• Specific lesions: fissures, fistulas, oral Crohn's disease, drug rashes</li><li>• Nutritional deficiencies: acrodermatitis enteropathica, purpura, glossitis, hair loss, brittle nails</li><li>• Associated diseases: vitiligo, psoriasis, amyloidosis</li></ul>
Hepatopancreatobiliary system	<ul style="list-style-type: none"><li>• Primary sclerosing cholangitis, bile-duct carcinoma</li><li>• Associated inflammation: autoimmune chronic active hepatitis, pericholangitis, portal fibrosis, cirrhosis, granulomatous disease</li><li>• Metabolic manifestations: fatty liver, gallstones associated with ileal Crohn's disease</li></ul>
Ocular system	<ul style="list-style-type: none"><li>• Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease</li></ul>
Metabolic system	<ul style="list-style-type: none"><li>• Growth retardation in children and adolescents, delayed sexual maturation</li></ul>
Renal system	<ul style="list-style-type: none"><li>• Calcium oxalate stones</li></ul>

## **1.5 DIAGNOSIS**

Currently, there is no universally accepted gold standard for the diagnosis of CD. Diagnosis is established by clinical evaluation, as well as a combination of endoscopic, histological, radiological, and biochemical investigations. For routine diagnosis of CD, genetic or serologic testing is not recommended (26).

### **1.5.1 History-taking and physical examination**

During the history-taking process, it is crucial to evaluate the characteristics of abdominal pain and diarrhea while also examining risk factors associated with Crohn's disease, such as smoking, family history, medication use, alcohol or drug consumption, and travel to areas with a high risk of parasite infections. In addition, extraintestinal conditions, joint problems, and perianal lesions should be considered. Alternative causes of diarrhea, such as food intolerance, bacterial overgrowth, celiac disease, and hyperthyroidism, should also be considered. It is essential to consider a history of appendectomy as well (26).

During the physical examination, it is important to observe objective signs of systemic toxicity such as fever, rapid heart rate, and low blood pressure. It is also necessary to assess hydration and nutrition and inspect the right lower abdomen for tenderness and rigidity. In addition, a thorough assessment of the perineal, anal, and rectal regions is required to identify external lesions such as skin tags, bulges, and fistula openings, as well as internal issues such as fissures, ulcers, stenosis, and secretions in the anal canal (9).

### **1.5.2 Lab Tests**

Although no laboratory test definitively rules out or diagnoses CD, anemia, iron deficiency, thrombocytosis, and an increase in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly found in blood tests of CD patients (1,9). CRP and ESR are laboratory markers frequently used for measuring inflammation in CD. Because of its short half-life, CRP correlates with disease activity and changes over time (26).

Low albumin levels and vitamin deficiencies, especially vitamin B12, are also common in CD, especially in patients with ileal complications (9).

Stool biomarkers such as fecal calprotectin are increasingly being used to screen for and assess disease activity in IBD. Fecal calprotectin levels reflect intestinal inflammation and are a reliable indicator of IBD with high accuracy. In individuals with irritable bowel syndrome-like symptoms, a fecal calprotectin level below 40 µg/g is associated with only a 1% risk of IBD (3). This biomarker can also guide the decision to perform endoscopic examinations, especially in children (26). After surgery, a fecal calprotectin level above 100 µg/g strongly predicts the likelihood of endoscopic recurrence (3). However, none of these inflammatory markers, including calprotectin, are specific enough to differentiate CD from ulcerative colitis or enteric infections.

Microbiological testing for infectious diarrhea including *Clostridium difficile* toxin is recommended (26).

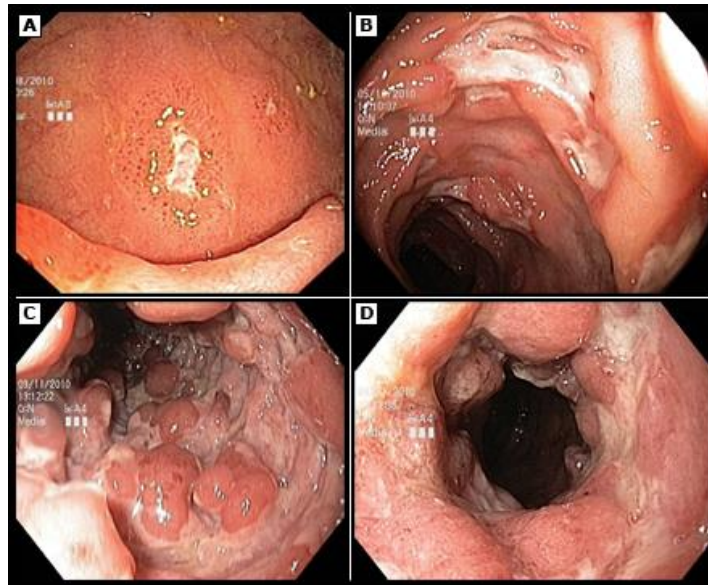
In some cases, serological testing may be used, but it should be noted that the available ASCA and ANCA tests are not highly accurate for routine diagnosis or distinguishing between colonic CD and UC (26). However, patients who present with high titers and increasing numbers of positive markers have an increased likelihood of developing more aggressive phenotypes (3).

Furthermore, despite advances in CD genetics, there are currently no genetic tests routinely recommended for diagnosis (26).

### **1.5.3 Endoscopy and biopsies**

Ileocolonoscopy, along with multiple biopsy samples, is established as the preferred initial diagnostic procedure for CD. It includes a complete examination with at least 2 biopsies taken from 5 segments, including both the ileum and colon (including the rectum), for all patients with CD (5,9,26)

Endoscopic findings are typically skipped lesions (3) with varying degrees of inflammation, including erythema, friability, erosions, and ulceration. Ulceration may vary in size and depth, ranging from small aphthous ulcers to linear and serpiginous ulcers surrounded by edematous mucosa. Inflammatory pseudopolyps, stenoses, and fistulas may also occur (1,9).



**Fig. 2** - Endoscopic findings in Crohn's disease include: aphthous ulcers, which are the earliest lesions seen in Crohn's disease (panel A); large ulcers interspersed with normal mucosa, which are typical for the segmental distribution of Crohn's disease (panel B); a cobblestone appearance that is characterized by nodular thickening, with linear or serpiginous ulcers (panel C); and strictures due to fibrosis (panel D) (35).

Complete colonoscopy carries an increased risk of perforating the bowel. An initial flexible sigmoidoscopy is safer, and an ileocolonoscopy should be delayed until the patient's condition has improved (3).

Capsule endoscopy and enteroscopy with biopsy are useful tools for diagnosing CD in selected patients with suggestive symptoms after failed radiological examinations.

Although lesions may affect any segment of the digestive tract, the most common areas of concern are the distal ileum (30-40%), distal ileum and colon (40-55%), or colon alone (5-10%).

Patients with CD, who experience symptoms such as dyspepsia, abdominal pain, and vomiting may benefit from upper GI endoscopy. Upper GI endoscopy may also be important in certain cases to establish a diagnosis, as localized gastritis may be a manifestation of CD. CD involving the upper gastrointestinal (GI) tract typically also involves the small or large bowel (26).

Patients with extensive Crohn's colitis have an elevated risk of colorectal cancer. To prevent and detect dysplasia, endoscopy with biopsy may be used (26).

The typical lesions are characterized by chronic, patchy, and transmural inflammation, marked by an increased presence of lymphocytes and plasma cells. Additionally, the crypts exhibit discontinuous irregularities, and noncaseating granulomas can be found in the lamina propria, although they are present in only 15-50% of biopsies and are not associated with active crypt lesions. When analyzing samples taken from the terminal ileum, irregularities of the villi may also be observed (9).

#### **1.5.4 Imaging**

Cross-sectional imaging (MRI and CT-Enterography) and trans-abdominal ultrasonography (US) are complementary to endoscopy and offer the opportunity to detect and stage inflammatory, obstructive, and fistulising CD.

All these techniques are superior to conventional barium studies in detecting stenotic lesions (26).

CTE and MRI are currently the standard methods for assessing the small intestine. These techniques can establish disease extension and activity based on wall thickness and increased intravenous contrast enhancement. The magnitude of these changes, along with the presence of edema and ulcers, allows for the categorization of disease severity. CTE is more widely available and less time-consuming than MRI (26). CTE and MRI scans of the small intestine require oral contrast for proper expansion of the area. While enteroclysis provides better distension than oral ingestion, it can cause discomfort and radiation exposure. When upper CD lesions are suspected and adequate distention cannot be achieved with oral contrast, enteroclysis may be necessary (26).

Ultrasound (US), with or without contrast agents such as gas or microbubble shells, is a noninvasive imaging modality that is widely available. Its sensitivity and specificity in diagnosing and evaluating Crohn's disease are comparable to those of MRI and CTE scans. The US is usually effective in visualizing the ileocecal, sigmoid, and often the ascending and descending colon in most patients.

Prospective studies have emphasized its effectiveness in initial diagnosis, assessing disease activity, and identifying complications such as fistulas, stenoses, and abscesses. A common sign of CD detectable in the US is increased bowel wall thickness (5,26).

Transrectal and endoscopic ultrasonography help assess perianal complications, but the preferred approach in such cases is pelvic MRI (3,5)

Direct radiological examination of the abdomen is still valuable in cases where occlusion is suspected, as it can help identify hydro-aerial levels and distention of ileal loops, as well as bowel perforation (25).

## **1.6 CLASSIFICATION OF CD**

Classification of Crohn's disease enables patients to be clustered into similar groups, helping to design specific treatment strategies. Classification can be based on the phenotype of the disease (Montreal Classification), the level of disease activity, and the response to treatment (9).

### *The Montreal classification*

The Montreal Classification, born as a revision of the Vienna Classification, has not changed the three dominant parameters of age at diagnosis (A), disease location (L), and disease behavior (B), but has introduced modifications within each of these categories (9,36).

Regarding age of onset, the Montreal classification includes a distinct A1 category for individuals diagnosed with the disease at or before the age of 16. The categories A2 and A3 correspond to the age of diagnosis between 17-40 and above 40 years, respectively. This significant change stems from research indicating higher prevalence rates of certain subtypes in early-onset Crohn's disease. (36).

Concerning the disease location (L), the Vienna Classification had a significant drawback. Each of the four identified locations was deemed mutually exclusive, meaning that upper GI disease could not coexist with a more distal location.

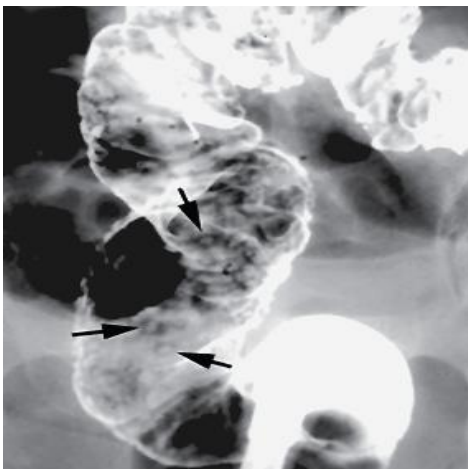
However, it's evident that upper gastrointestinal disease can be common and could coexist with ileal and colonic disease. Thus, the revised Montreal classification no longer deems these parameters as mutually exclusive.

About 35-45% of patients exhibit involvement of the terminal ileum and proximal colon, while 30% indicate solely small intestine involvement (typically at the ileum level), and 20% solely colon involvement (5).

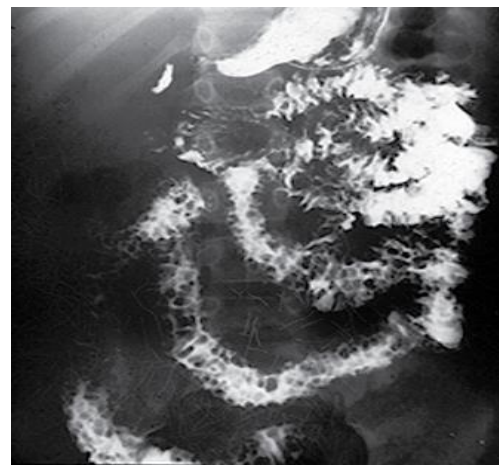
In addition, 25% of patients experience perianal complications such as fissures and fistulas. Less commonly (<10%), patients may exhibit singular perianal symptoms, upper gastrointestinal disease, or extraintestinal manifestations (EIMs) of the disease (1).

Crohn's disease has been classified into different phenotypic subtypes for research and treatment purposes, including inflammatory, sclerosing, and fistulizing forms. (1). The introduction of the perianal disease category as a separate classification was the main change from the previous classification (36).

Inflammatory CD is characterized by inflammation of the gastrointestinal tract with wall thickening but without stricturing or fistulizing features. This form is marked by the presence of small, shallow ulcers (aphthoid ulcers) that indicate recent disease onset (Fig.3), or deeper ulcerations and fissures. These deeper ulcerations can connect and are surrounded by swollen mucosa, giving rise to a distinctive "cobblestone" appearance (Fig.4).



*Fig.3 - Double contrast barium enema demonstrates small aphthoid ulcers in a patient with early Crohn's disease of the colon (arrows) (36).*



*Fig.4 - Cobblestone appearance in Crohn's disease. This cobblestone appearance is produced by barium being dispersed between the edematous inflamed mucosa (36).*

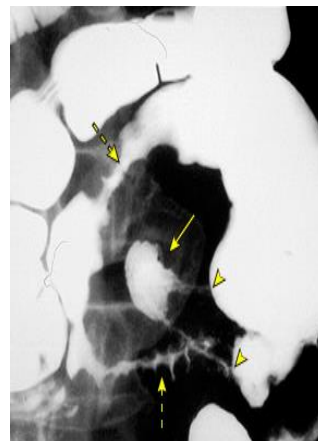
Over time, inflammation may lead to fibrosis and narrowing of the passage, resulting in stricturing disease due to the fibrotic outcome of the ulcerations and wall inflammation (Fig.5).

Stenoses may be single or multiple of variable length, and often located in the distal ileum, associated with dilatation of the proximal loops. Once fibrosis occurs, surgery is the only way to reverse it.

Persistent transmural inflammation can give rise to the development of fistulas, which are abnormal tracts connecting the bowel to nearby organs, such as the vagina, bladder, or other areas of the bowel. Fistulas may also extend into the retroperitoneum or, more commonly, into the mesentery, resulting in an abscess (Fig.6) (5,25).



**Fig.5** - Small bowel follow through study shows marked narrowing, irregularity, and ulceration in the distal ileum (arrows) in a patient with Crohn's disease (36).



**Fig.6** - Small bowel follow through study demonstrates an abscess cavity (arrow) with fistulae connecting the cavity to the adjacent small bowel (arrowheads). Note the marked thickening of the inflamed mucosal folds (dashed arrows) (36).



**Table 2** – The Montreal classification and the previous Vienna Classification (36).

	Vienna	Montreal
Age at diagnosis	A1 below 40 y A2 above 40 y	A1 below 16 y A2 between 17 and 40 y A3 above 40 y
Location	L1 ileal L2 colonic L3 ileocolonic L4 upper	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifier†
*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present. †“p” is added to B1–B3 when concomitant perianal disease is present.		

### *Activity index*

There are several clinical activity indices used to measure the level of intestinal inflammation in Crohn's disease. For the inflammatory pattern, commonly used clinical indices include the Crohn's Disease Activity Index (CDAI), the simpler and widely used Harvey-Bradshaw index in routine practice, and the van Hees index.

The Harvey-Bradshaw index is based on only five items:

- A. General wellbeing (0=very well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible).
- B. Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe).
- C. Number of liquid stools per day.
- D. Abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender).
- E. Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item).

Patients are asked to score these items for the previous day, and this is a simpler alternative to the CDAI and it does not require any biochemical testing (37).

Endoscopic indices are utilized for evaluating lesions since mucosal healing decreases the necessity of glucocorticoids, hospitalizations, and surgical procedures. The widely accepted endoscopic indexes are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and its simplified version known as the Simple Endoscopic Score Crohn's Disease (SES-CD) (9,37).

### *Response to treatment*

The classification of Crohn's disease based on response to treatment includes two main categories: cortico-refractory and cortico-dependent.

Cortico-refractory is defined as the persistence of inflammatory activity even after receiving treatment with prednisone (or an equivalent) at full dosages (1 mg/kg/day) for 4 weeks.

Cortico-dependent: This classification applies to situations in which it is impossible to lower glucocorticoid medication below a specific dose equivalent to 10 mg/day of prednisone (or 3 mg/day of budesonide) within the first 3 months of treatment without experiencing symptom recurrence. Additionally, it can be categorized as experiencing relapse within the first 3 months after stopping corticosteroid treatment (9).

## **1.7 MEDICAL TREATMENT**

### *Induction therapy*

For the management of mild-to-moderate Crohn's disease, budesonide has shown effectiveness in achieving remission. Long-term steroid use is constrained by side effects and the inability to prevent disease relapse. Combining thiopurines with steroids has been demonstrated to be effective in steroid-dependent patients, as thiopurines alone are insufficient. On the other hand, 5-ASA compounds and Sulphasalazine do not have a therapeutic effect.

For patients with moderate-to-severe CD who are unresponsive to conventional therapy (steroids and/or thiopurines), monoclonal antibodies (such as anti-TNF agents, Ustekinumab, or Vedolizumab) are recommended.

Combination therapy of Infliximab with thiopurines is more effective than Infliximab alone for achieving steroid-free remission in treatment-naive patients. However, the selection of therapy should account for patient characteristics, costs, and local availability.

Ustekinumab and Vedolizumab are recommended for patients who do not respond to anti-TNF therapy. There is limited direct evidence regarding the comparison between these agents, and personalized risk assessment is essential in determining the treatment approach.

Surgery may be considered as an alternative option for patients with moderate-to-severe Crohn's disease with a limited disease extent or those who do not respond to at least one monoclonal antibody. Clinicians typically base initial treatment on the perceived severity of the disease and patient-specific factors. Additional research is required to evaluate early biological use, highlight the importance of preventing complications and disease modification, and validate risk factors for disease progression (38).

#### *Maintenance strategies*

Immunosuppressants and biologic agents are the most effective in maintaining medically induced remission in patients with moderate to severe Crohn's disease (CD). Amino-salicylates and steroids aren't advised for maintenance purposes as they lack efficacy and present long-term risks. Steroid-dependent CD patients are recommended to maintain remission via Thiopurines and methotrexate.

However, there is insufficient evidence supporting the long-term use of thiopurines due to an increased risk of lymphoma and skin cancer. Thus, regular monitoring is crucial.

For patients in remission using a biologic agent-based strategy, it is recommended to continue using the same agent for maintenance. There is inadequate evidence to support either the continuation or withdrawal of anti-TNF therapy in CD patients after attaining long-term remission; therefore, the decision should be personalized and discussed with the patient.

There is a significant research gap regarding the prolonged management of patients in remission (38).

## **1.8 SURGICAL TREATMENT**

Despite significant advances in medical therapy for Crohn's disease, surgery still plays a fundamental role in its management. It is widely recognized that approximately 50-60% of patients with Crohn's disease will require at least one surgical resection within a decade of their initial diagnosis (39). However, surgery does not provide a definitive cure for the disease, resulting in a high incidence of relapse in many patients. After ileocecal resection, endoscopic recurrence can be seen in 70-90% of patients and its severity can determine the likelihood of clinical recurrence. Surgical intervention is required in approximately 40% of patients at five years and 55% of patients at ten years after initial surgery. Furthermore, for 5-15% of patients, a third surgery is needed. At last, around 12% of patients eventually need a permanent ostomy (40).

### **1.8.1 Surgical indications**

Indications for surgery in Crohn's disease include acute and chronic complications as well as failure of medical therapy.

The need for surgical intervention is highest when medical therapy has failed, as demonstrated by persistent or worsening symptoms despite optimal treatment or the emergence of side effects in conjunction with limited patient adherence to the prescribed regimen (40).

Chronic complications may involve non-reversible narrowing of intestinal lesions, as well as the development of neoplasia in the colon or small intestine, and fistulization.

In certain cases, surgical intervention may become an emergency due to acute conditions such as perforated peritonitis, toxic colitis, hemorrhage, abscess formation, or septic shock. If an abdominal abscess is present, antibiotics combined with either percutaneous or surgical drainage of the collection is preferred, with resective treatment deferred if possible (25,41).

Another situation in which surgery could be necessary is intestinal obstruction, a common complication in Crohn's disease. Non-surgical measures are the primary approach to resolving obstruction, such as using a nasogastric tube and systemic anti-inflammatory therapy, which have been effective in most cases. If necessary, elective surgery can be considered, potentially using a minimally invasive technique (25).

### **1.8.2 Small intestinal or ileocolonic surgery**

#### *Resection*

The terminal ileum is commonly affected in patients with Crohn's disease (CD), and an ileocolonic resection (ICR) is often recommended for a complicated CD or as an alternative to medical therapy in cases of short segment inflammatory ileal CD (42).

Initially, the traditional management of the disease involved excising lesions along with a substantial amount of healthy bowel tissue. However, due to the high rate of postoperative recurrence, even after complete removal of macroscopic lesions, the focus has shifted from a "radical" approach to one that emphasizes the preservation of as much of the bowel as possible.

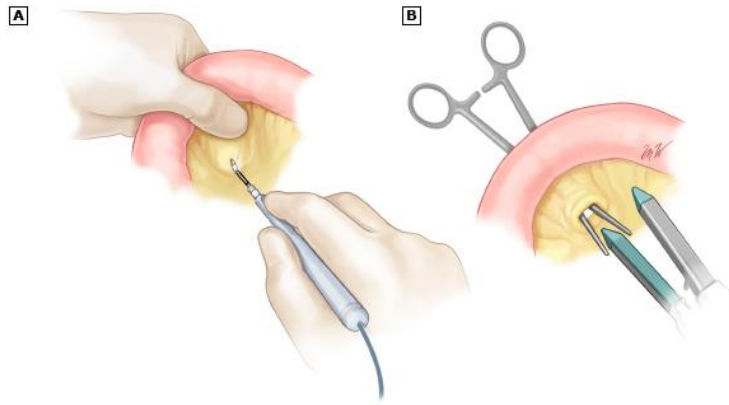
This is supported by the fact that multiple studies have shown that the recurrence of the disease after bowel resection is not affected by microscopic disease involvement at the resection margins (43).

Currently, the widely used approach for necessary resections is to dissect the bowel within macroscopically healthy areas, while staying no more than 2-3 cm away from macroscopically visible lesions to minimize bowel loss (44).

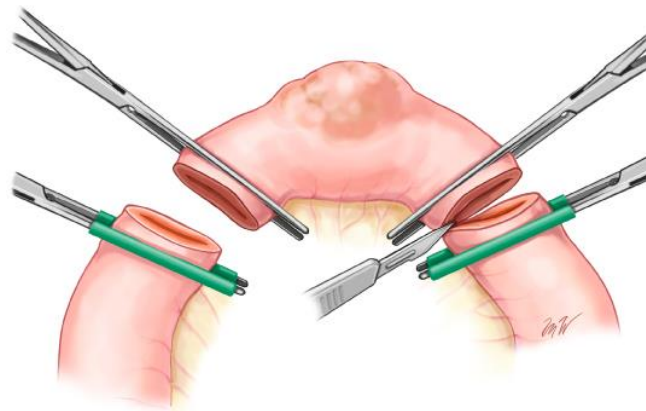
Excessively extensive intestinal resections, particularly in patients undergoing multiple surgeries, may cause "short bowel syndrome."

This condition results in significant nutritional problems as a result of an insufficient residual length of the small intestine, which is essential for adequate food absorption (40).

For patients with extensive disease affecting long segments (over 100 cm) or those who have undergone previous surgeries, strictureplasty has also been implemented in clinical practice (44).



**Fig.7** - Bowel resection using a linear suture machine. Here, the surgeon thins the mesentery below the resection line. Afterwards, a small mesenteric defect is created with electrocautery, and the stapler jaw is inserted through this defect for resection (45).

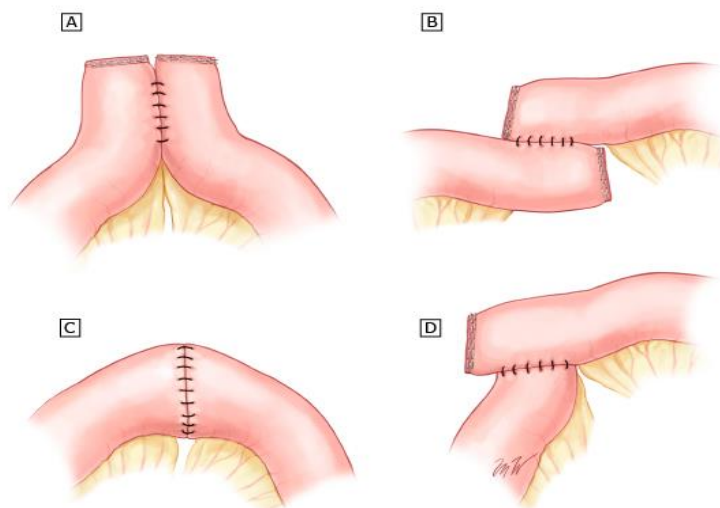


**Fig.8** - Another technique involves non-crushing bowel forceps which are positioned obliquely on either side of the pathologic area. The bowel is then transected with a scalpel. Angling the resection line obliquely is necessary to ensure a longer mesenteric border than the anti-mesenteric border. This will ensure a sturdy blood supply to the anti-mesenteric area of the anastomosis that is at higher risk of ischemia (45).

### 1.8.3 Anastomosis

Restoring digestive continuity after small bowel or ileocecal resection involves either manual or mechanical anastomosis, which can be side-to-side, side-to-end, or end-to-end (40):

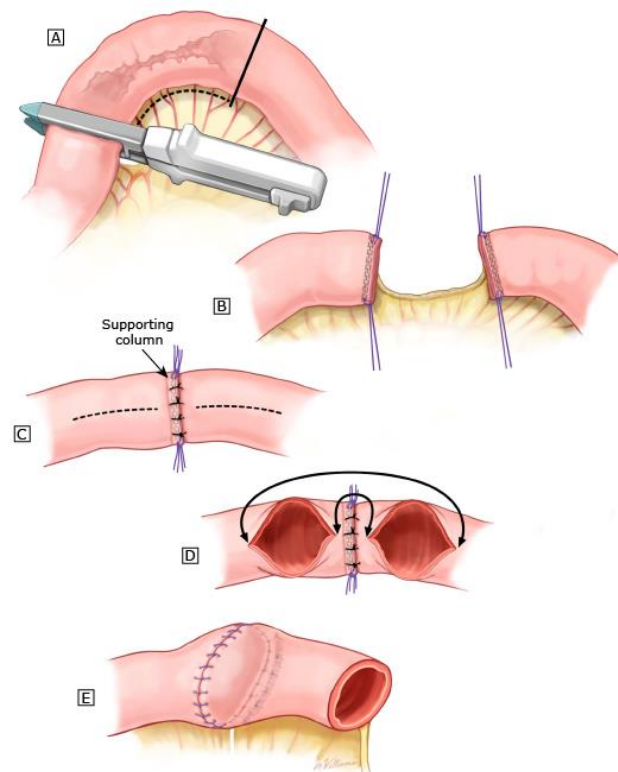
- End-to-end anastomoses (EEA) replicate normal gastrointestinal motility in which the ends of the two stumps are directly aligned (45).
- End-to-side anastomosis (ESA) is a technique typically used when there is a size discrepancy between the bowel loops to be joined, such as in enterocolostomy or following small bowel obstruction with significant proximal distension. To perform this technique, the end of one loop of the bowel is carefully anastomosed into the side of another at the antimesenteric border (small bowel) or one of the taeniae (colon). Sewing to the antimesenteric border minimizes ischemia while sewing to the taeniae adds strength to the reconstruction and avoids diverticula if they are present.
- Side-by-side anastomosis (SSA): the loops of the bowel can be positioned either side by side or in an overlapping configuration. The enterotomy is performed in the antimesenteric border to minimize ischemia. The anastomosis can be made by a linear stapler or handsewn (single or double layer) (45).



**Fig.9** - Types of bowel anastomosis:

(A) Side-to-side, antiperistaltic configuration; (B) side-to-side, isoperistaltic configuration; (C) end-to-end anastomosis; (D) end-to-side anastomosis(45).

- Kono-S anastomosis is a novel functional end-to-end hand-sewn technique, which is performed on the antimesenteric side. To avoid devascularization and denervation of the remaining intestine, the mesentery near the intestinal loop to be removed is divided at the mesenteric wall of the intestine with a vessel sealing system. Bowel resection is then performed using GIA staplers positioned perpendicular to the mesentery (A). The bowel stumps are first reinforced with absorbable sutures, then sutured together to create a common support column, a unique feature of this technique (B and C). Two longitudinal incisions are then made on the anti-mesenteric side, 1 cm away from the support column (D). The anastomosis is created transversely by using a single-layer handsewn suture (E). In the completed anastomosis, the support column is positioned between the anastomosis and the mesentery. This anastomotic configuration potentially maintains intestinal diameter, thereby preventing distortion or stenosis associated with recurrent strictures that often originate from the mesenteric side of the lumen (46).



**Fig.10 - Kono-S anastomosis (46)**



The anastomosis can be created using a linear cutter stapler or by manual suturing. The stapled side-to-side anastomosis is currently the preferred technique recommended by the European Crohn's and Colitis Organization (47,48). A wider lumen is suggested by these guidelines and may potentially reduce the incidence of postoperative recurrence (48).

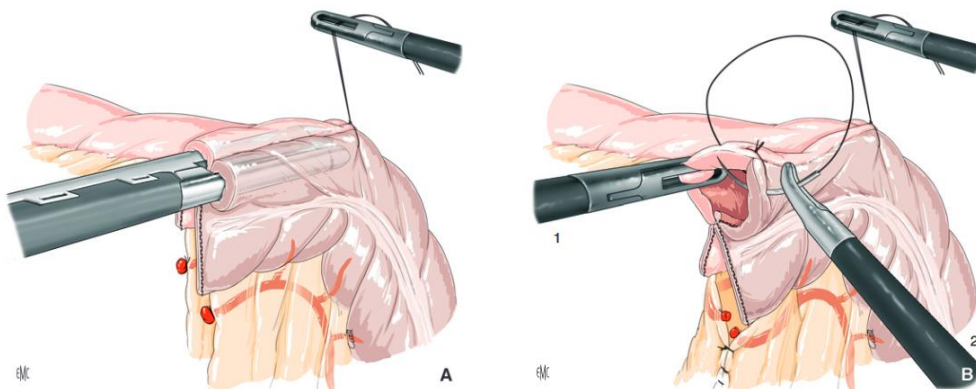
As per Similis et al.'s meta-analysis, EEA was linked to a higher risk of anastomotic leaks than other anastomotic configurations. In contrast, SSA showed a lower incidence of anastomotic leakage and fistula, fewer overall postoperative complications, shorter hospital stays, and a perianastomotic recurrence rate similar to EEA (41). In emergency operation patients, an EEA carries a higher likelihood of early postoperative endoscopic recurrence, along with smoking and failure to initiate early medical prophylaxis (48).

No significant differences in terms of complications have been observed between manual and mechanical anastomosis. However, it appears that cases of mechanical anastomosis have a lower recurrence rate (41).

#### *Intracorporeal vs extracorporeal anastomosis*

In addition to the differences listed above, anastomoses can be further classified as either intracorporeal or extracorporeal.

The intracorporeal anastomosis is performed within the abdominal cavity. Once the pathological bowel is resected and removed via suprapubic the stapled stumps must be appropriately aligned using a serosal stitch. Two enterotomies are then made in the ileal and colic regions as back ports for the linear mechanical stapler that will create a mechanical, isoperistaltic ileocolic, ileo-colic, side to side (SS) anastomosis. The introductory enterotomy is closed with a 3/0 thread suture (Fig.10) (49).



**Fig.11** – Intracorporeal mechanical ileocolic anastomosis (49).

The extracorporeal anastomosis can be performed either by laparotomy or by laparoscopy. Laparoscopy usually involves a small periumbilical mini-laparotomy (or Pfannenstiel incision) to exteriorize the colic end and the last ileal loop, which has been previously mobilized. At this stage, either a stapled or hand-sewn double-layer isoperistaltic or anisoperistaltic anastomosis may be performed.

Currently, there are no studies in the literature comparing these two techniques in terms of complications, recurrence, body image, disease activity, or quality of life (49).

#### *Laparoscopy vs laparotomy*

According to ECCO Statement 7F, the preferred method for bowel resection is the laparoscopic approach, with laparotomy reserved for patients with multiple operations or complications (ECCO). Both techniques demonstrate comparable morbidity and recurrence outcomes. However, the laparoscopic approach offers clear advantages over open surgery (40). Specifically, it has been shown to reduce postoperative adhesions, shorten hospital stays, expedite recovery, lower overall postoperative complications, decrease small bowel obstructions, reduce postoperative hernias, and enhance cosmetic outcomes. The cost is also lower. The results can be improved by employing the single-port laparoscopic approach. This approach is particularly advantageous for younger, more active patients who may require re-operation due to disease recurrence.

Currently, laparotomy is recommended for patients with both stenotic disease and complex cases, such as perforating forms with abscesses or enteroenteric or enterovesical fistulas. Additionally, it is increasingly used for recurrent disease at sites of prior laparoscopic anastomosis (39).

## *Strictureplasty*

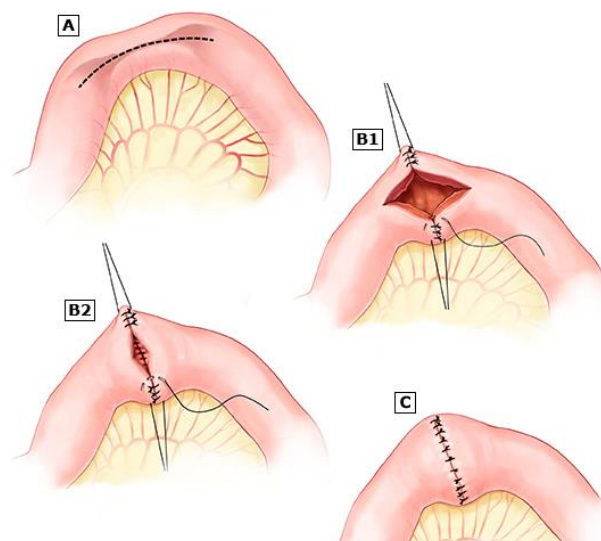
Strictureplasty is a useful surgical option for various Crohn's disease cases. It is particularly recommended for duodenal stenosis, skip lesions, extensive forms, and patients who have a history of long bowel resection (44).

The main objective of strictureplasty is to preserve intestinal tissue by enlarging and releasing strictures rather than removing sections of the intestine (43). As per the ECCO statement, it is the preferred treatment for multiple fibrotic strictures of the small intestine (47).

Over time, many strictureplasty techniques have been developed, categorized as either conventional or non-conventional methods. Conventional strictureplasties include the Heineke-Mikulicz and Finney procedures. Ileo-ileal isoperistaltic stricturoplasty, also referred to as Michelassi stricturoplasty is considered a non-conventional stricturoplasty (47).

For strictures less than 10 cm in length, conventional strictureplasty is recommended. However, non-traditional strictureplasties may be considered in cases of extensive disease with long stricture segments where resection would prevent adequate small bowel length (39).

- The Heineke-Mikulicz method is used for treating less extensive stenoses (44) and involves a longitudinal incision that exceeds the length of the stricture by 1-2 cm at the antimesenteric border, followed by transverse suturing with 2-layer closure using a continuous long-term absorbable suture (Fig.11) (39).



**Fig.12** - A full-thickness longitudinal incision is made along the antimesenteric border of the stricture for approximately 1 to 2 cm beyond the stricture.

- For longer stenoses between 10 and 20 cm, a Finney strictureplasty may be recommended. This procedure involves a longitudinal incision on the anti-mesenteric border and a side-to-side hand-sewn or stapled anastomosis (39).
- The handsewn side-to-side anastomosis technique, known as the isoperistaltic strictureplasty, has been previously described by Michelassi et al. (39) and is used to treat long stenotic segments or multiple strictures (47). This process entails dividing the stenotic loop with its mesentery at approximately half its length, sliding the proximal portion over the distal part, performing a longitudinal separation, and then suturing the two adjacent stenotic loops (44) with a handsewn side-to-side anastomosis (39).



*Fig.13 - Side-to-side isoperistaltic strictureplasty (Michelassi) (46)*

The Heineke-Mikulicz method is the most frequently (over 90%) employed conventional stricturoplasty. On the other hand, the Michelassi method is the predominant non-conventional stricturoplasty (over 80%). The Finney technique is associated with higher recurrence rates, probably due to the formation of a large lateral diverticulum with fecal impaction and bacterial overgrowth (47).

Strictureplasty has proven to be a reliable and efficient technique for treating jejunoileal Crohn's disease while preserving the integrity of the small bowel.

It is best suited for cases of multiple, recurrent, or long stenoses. Nonetheless, this approach does not target the affected area, and those with an extended history of CD ought to be wary of developing malignancies. In a meta-analysis comparing strictureplasty to resection in small bowel CD, postoperative complications were less frequent with strictureplasty, but surgical recurrence was more likely to occur (39).

Complications after strictureplasty may include small bowel obstruction, intra-abdominal septic complications, suture leakages, and intra-luminal or intra-abdominal bleeding, with a cumulative reoperation rate of 2.8%. Factors such as malnutrition, hypoalbuminemia, unscheduled surgery, intra-abdominal septic complications with peritoneal contamination, anemia, older age, and preoperative weight loss may impact postoperative complications (47).

Contraindications for strictureplasty include suspected malignancy, forms with particularly fragile and bleeding mucosa, deep ulcers, those linked to abscesses or complex fistulizing disease, and colic stenosis (44).

#### **1.8.4 Colonic surgery**

The surgical management of Crohn's disease in the colon is still controversial. Depending on the clinical presentation or location of the disease, some specialists suggest different surgical techniques. The recommended surgical options consist of total proctocolectomy (TPC), subtotal colectomy (STC) with ileorectal anastomosis, segmental colectomy (SC), and restorative proctocolectomy (RPC) with ileal pouch reconstruction.

TPC involves complete removal of the colon and rectum and has demonstrated low recurrence rates, making it a desirable option to reduce the risk of recurrence.

Nevertheless, TPC carries substantial chances of complications in the perineal wound and stoma and results in permanent stoma formation, which impairs the patient's quality of life.

STC with ileorectal anastomosis (IRA) is a more conservative approach that avoids the removal of the rectum, but the patient still faces the possibility of anastomotic or rectal recurrence.

In colonic Crohn's disease, SC enables patients to avoid a stoma, but it also raises the risk of anastomotic and remnant colon recurrence. This increases the chances of requiring further surgery.

It is unclear whether SC or colectomy with ileorectal anastomosis (IRA) is the better option, especially when multiple segments are involved.

RPC with ileal pouch reconstruction has been proposed in selected patients without small bowel disease and a healthy anus.

However, this approach is still relatively uncommon and subject to debate due to the high risk of pouch failure, leading to pouch excision. Many dedicated centers do not offer this option to patients who have been diagnosed with CD before surgery.

Based on Angriman et al.'s 2017 meta-analysis, both STC and SC are equally effective treatments for colonic CD in patients with colitis and minimal or no perianal disease. The surgical technique used should be based on the number of lesions and the extent of colonic involvement. STC is the preferred option when two or more segments are involved (50).

### **1.8.5 Disease recurrence**

While surgery can alleviate symptoms and improve the immediate quality of life for patients, it does not provide a cure (51).

Disease recurrence in Crohn's disease (CD) can reach up to 35% following colectomy and ileostomy, and the risk appears to be even greater with ileocolonic resection (ICR) and ileocolonic anastomosis (ICA) (52). Several studies have demonstrated that postoperative endoscopic recurrence occur in 30% to 85% of patients at the new terminal ileum proximal to the primary anastomosis within one year after the operation (51).

For an accurate discussion of recurrence, there must be a distinction between clinical recurrence, endoscopic recurrence, and surgical recurrence (53).

#### *Endoscopic recurrence*

According to the 2017 American Gastroenterological Association (AGA) guidelines, postoperative endoscopic surveillance is recommended within 6-12 months after surgery for Crohn's disease in patients with or without postoperative medical therapy for CD (54).

Endoscopic recurrence can be observed in nearly 35%-85% of patients at the neoterminal ileum within 12 months of surgery and is almost inevitable by 5 years. (53,55).

Endoscopic recurrence is defined by the presence of visible inflammation and ulceration. These macroscopic changes are detected during planned postoperative endoscopy and are classified according to Rutgeerts' score (56).

The Rutgeerts Score (RS), developed in the early 1990s, is a valuable tool for predicting postoperative recurrence in patients with Crohn's disease following ileocecal resection (ICR) and ileocolonic anastomosis (ICA).

This classification system categorizes endoscopic findings into five distinct groups (i,0–i,4) based on the severity and extent of lesions present at the anastomosis and neo-terminal ileum. This method has shown a strong correlation with endoscopic recurrence following surgical procedures. Notably, patients with low-grade mucosal inflammation (i,0 and i,1) showed a symptomatic recurrence rate of 9% over a 7-year period, whereas those with high-grade disease (i,3 and i,4) experienced an almost 100% symptomatic recurrence rate within 4 year (52,57).

**Table 3** – Rutgeert’s score

Rutgeerts’ score	Endoscopic description of findings
i0	Absence of lesions
i1	≤5 aphthous ulcers
i2	>5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions, or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with larger ulcers, nodules, and/or narrowing

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*Rutgeert’s score ≥ i2 defines endoscopic recurrence. Adapted from Rutgeert’s et Al (57).*

### *Clinical recurrence*

Clinical recurrence, as defined by the Crohn's Disease Activity Index (CDAI), affects between 10% to 38% of patients within 12 months after surgery and 35% to 50% of patients within 5 years (53). The Crohn's Disease Activity Index is a scoring system utilized for assessing the severity of Crohn's disease.

It is based on the assessment of eight variables, six of which are objective parameters, including body weight, hematocrit, number of liquid stools in the previous week, the requirement for opioid antidiarrheal medication, the existence of extraintestinal complications, and the detection of an abdominal mass (verified by a healthcare professional). Additionally, the evaluation includes two parameters that rely on the patient's perception: the general well-being experienced in the preceding seven days (rated from 0 = excellent to 4 = very poor) and any abdominal pain experienced during the previous week (rated from 0 = none to 3 = severe) (58).

However, the Harvey-Bradshaw index is also widely used to assess disease activity. Although it is a simplified version of the CDAI, it is equally effective and does not require biochemical testing (37).

### *Surgical recurrence*

The postoperative CD that necessitates another intestinal resection, known as surgical recurrence, occurs in about 25% of patients after 5 years and 35% after 10 years of the initial surgery (53).

It has been suggested that the type of anastomotic configuration and luminal diameter may influence the development of postoperative recurrence, as a significant amount of disease activity occurs near the original surgical anastomosis. Currently, there is a preference for using a wide colonic anastomosis technique with a stapled side-to-side anastomosis.

This approach is preferred because it prevents early stricture, retrograde flow of bowel contents, fecal impaction, and reduced blood supply.

Additionally, studies report a correlation between this method and a lower incidence of postoperative complications, including anastomotic leaks (54,56).



### *Risk factors for recurrence*

Numerous demographic and pathological factors have been studied to understand their potential impact on CD recurrence.

Factors such as gender, family history, symptoms, presence of granulomas, 'stricturing' or fistulizing CD, surgical margin length, microscopic disease at the surgical margin, location and extent of disease, type of surgery, and several anastomoses have not provided conclusive evidence regarding their involvement in recurrence (59).

The most significant risk factor for postoperative recurrence (POR) in Crohn's disease (CD) is active smoking. Other risk factors include perianal lesions, penetrating behavior, prior intestinal resection, and extensive bowel resection (Buisson et al.). Possible additional risk factors are a brief interval between the diagnosis and surgery (<10 years) and youthful age (<30 years) at the disease diagnosis (53).

According to Scarpa et al., elevated TGF- $\beta$ 1 levels in patients with Crohn's disease who have had ileocolonic resection are linked to early clinical disease recurrence. However, there is no association between IGF-1 and the recurrence of Crohn's disease (60).

Due to the high recurrence rates after surgical resection in patients with Crohn's disease (CD), several approaches have been studied to minimize the long-term risk of disease recurrence. These strategies include early postoperative pharmacologic prophylaxis administered a few weeks after surgical resection using a variety of pharmacologic agents. Additionally, regular endoscopic surveillance and a treatment escalation plan are necessary within 6 to 12 months of surgery in cases of asymptomatic endoscopic recurrence (53).

## **2. AIM OF THE STUDY**

In Crohn's disease surgery remains necessary for most cases, especially in complication management. Intestinal resection of the terminal ileum followed by ileo-colic anastomosis is the most performed surgery for Crohn's disease since it typically affects the terminal ileum. Among the different types of anastomoses, mechanical side-to-side anastomosis is currently recommended by ECCO guidelines, and the laparoscopic method appears to be preferred. However, it remains uncertain whether performing the anastomosis intracorporeally or extracorporeally ultimately affects postoperative outcomes, leaving the decision up to the surgeon. Currently, there are no studies in the literature comparing these outcomes in ileocolic anastomoses.

Therefore, our study aims to investigate any differences between the two operation times in terms of disease activity, body image, quality of life, post-surgical complications, and clinical and surgical recurrence.

### 3. MATERIALS AND METHODS

#### 3.1 STUDY DESIGN

In this retrospective observational study, we reviewed the medical records of the patients who underwent ileocolic resection for Crohn's disease in our surgical department from 2020 to 2023. It results in a population of fifty patients. For each patient, surgical records, discharge letters, and outpatient follow-up visits were thoroughly analyzed. In July 2023, 48 patients were contacted and agreed to participate in a telephone interview. The purpose of the telephone interview was to assess patients' clinical disease activity (Harvey-Bradshaw), quality of life (Cleveland Global Quality of Life), and body image (Body Image Questionnaire) after bowel surgery. The study followed ethical standards and was approved by the local ethics committee.

#### *Harvey Bradshaw's index*

Clinical disease activity was measured using Harvey-Bradshaw's index (37).

**Table 4** – The Harvey Bradshaw's index (9).

Variables	Points
1. Overall status	0 Very good 1 Regular 2 Bad 3 Very bad 4 Bad
2. Abdominal pain	0 No 1 Mild 2 Moderate 3 Intense
3. Number of daily liquid stools	N points
4. Abdominal mass	0 No 1 Dubious 2 Defined 3 Defined and painful
5. Complications	1 Arthralgias 1 Uveitis 1 Erythema nodosum 1 Aphthous ulcer 1 Pyoderma gangrenosum 1 Anal fistula 1 Other fistulas 1 Abscesses

HBI Score: Remission: <5; Mild Disease: 5 to 7; Moderate Disease: 8 to 16; Severe Disease: >16.

### *Cleveland Global Quality of Life*

The Cleveland Global Quality of Life (CGQL) score consists of three items: current quality of life, current quality of health, and current energy level, each scored on a scale from 0 (worst) to 10 (best). The questionnaire is reported below.

Q1. Current Quality of Life (circle one):

1      2      3      4      5      6      7      8      9      10

Q2. Current Quality of Health (circle one):

1      2      3      4      5      6      7      8      9      10

Q3. Current Energy Level (circle one):

1      2      3      4      5      6      7      8      9      10

### *The Body Image Questionnaire*

The focus of the Body Image Questionnaire was to comprehend patients' post-surgery perceptions of themselves and their bodies, as well as to assess scar quality and the enhancement of overall self-esteem compared to their preoperative state. The questionnaire is reported below.

BIQ1. Are you less satisfied with your body since the operation?

range: 1 = no, not at all

2 = a little bit

3 = quite a bit

4 = yes, extremely

BIQ 2. Do you think the operation has damaged your body?

range: 1 = no, not at all

2 = a little bit

3 = quite a bit

4 = yes, extremely

BIQ 3. Do you feel less attractive as a result of your disease or treatment?

range: 1 = no, not at all

2 = a little bit

3 = quite a bit

4 = yes, extremely

BIQ 4. Do you feel less feminine/masculine as a result of your disease or treatment?

range: 1 = no, not at all

2 = a little bit

3 = quite a bit

4 = yes, extremely

BIQ 5. Is it difficult to look at yourself naked?

range: 1 = no, not at all

2 = a little bit

3 = quite a bit

4 = yes, extremely

BIQ 6. On a scale from 1 to 7, how satisfied are you with your (incisional) scar?

1 = very unsatisfied	2	3	4 = not unsatisfied/ not satisfied	5	6	7 = very satisfied
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BIQ 7. On a scale from 1 to 7, how would you describe your (incisional) scar?

1 = revolting	2	3	4 = not revolting/ not beautiful	5	6	7 = beautiful
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BIQ 8. Could you score your incisional scar on a scale from 1 to 10?

BIQ 9. How confident were you *before* your operation?

range: 1 = not very confident

10 = very confident

BIQ 10. How confident were you *after* your operation?

range: 1 = not very confident

10 = very confident

### *Post-operative complications*

Patients' discharge letters and medical records were reviewed to assess operative complications within 30 days of surgery, and the Clavien-Dindo classification was used to evaluate the severity of complications (61)

**Table 5** – The Clavien-Dindo classification (61).

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

\*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.  
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

## **3.2 INCLUSION AND EXCLUSION CRITERIA**

Our study included all consecutive patients diagnosed with CD who underwent ileocecal resection with side-to-side anastomosis in our department between April 2020 and July 2023. Patients without a confirmed diagnosis of CD, who underwent surgical procedures other than ileocecal resection, and who were not given side-to-side anastomoses to restore bowel continuity, were excluded from this study.

## **3.3 DATA COLLECTION**

The following data were collected for each patient enrolled in the study: date of birth, sex, age at CD diagnosis, age at operation, CD duration, symptoms at diagnosis, location of the disease, CD phenotype, indication for surgery, surgical details (laparoscopy/laparotomy approach, anastomosis configuration, handsewn/stapled anastomotic suture, intracorporeal/extracorporeal anastomosis, operating time), complications that occur within 30 days after surgery, HBI, CGQLand BIQ scores, pre-and postoperative therapy, clinical and surgical recurrence, medical treatment/reoperation for recurrence, follow-up duration.

Data were collected in a digital database created with Microsoft® Excel® for Microsoft 365 MSO, which was completed in July 2023.

### **3.4 SURGICAL TECHNIQUE**

The ileocolonic resection was performed removing all grossly involved bowels through a standard mid-line laparotomy or with laparoscopy assistance. The effectiveness of the macroscopical radicality was assessed by histological analysis, which showed that the histological disease activity at the resection margin was absent or very mild. To perform an intracorporeal anastomosis, the colon and ileum were transected with a mechanical stapler under laparoscopic guidance. An isoperistaltic mechanical side-to-side ileocolic anastomosis was then performed with one 60-mm linear stapler purple charged Signia™ (Medtronic Italia SpA Milano, Italia). The introductory enterotomy is closed with a barbed absorbable thread (V-Loc™ 180, Covidien, Mansfield, MA). The operative specimen was then extracted via Pfannenstiel incision.

To perform an extracorporeal anastomosis, the distal ileum and the right colon were fully mobilized and exteriorized by a 4–6 cm vertical incision through the umbilicus. In the case of the entero-sigmoid fistula or large inflammatory mass, a small Pfannenstiel incision (8 cm) was used instead of the trans-umbilical incision. Vascular ligation, bowel division, and anastomosis were performed extracorporeally. Handsewn isoperistaltic side-to-side anastomoses were performed layer-by-layer for a total length of 7-8 cm: the inner layer (mucosal) was anastomosed with a running suture of 4-0 PDS, (Ethicon, Somerville, NJ, USA) and the outer layer (seromuscular) was sewn with a running suture of 4-0 PDS.

### **3.5 STATISTICAL ANALYSIS**

The statistical analysis was performed using both Microsoft Excel and Origin 2018b 64-bit software (Northampton, Massachusetts, USA). Continuous data were expressed as median (range), and categorical data were expressed as frequency and percentage. Frequency analysis was performed using the Chi-square Test (Fisher exact test), while continuous data were compared with the Mann-Whitney U test. Actuarial recurrence analysis was performed comparing intracorporeal and extracorporeal anastomoses and Kaplan Meier curves were drawn.

A level of  $p < 0.05$  was considered significant in all the analyses and Bonferroni adjustment was used where appropriate.

## 4. RESULTS

### 4.1 PATIENTS' CHARACTERISTICS

In our department, between April 2020 and July 2023, 50 patients diagnosed with CD underwent ileocecal resection followed by a side-to-side ileocolonic anastomosis. 26 of them were male (52%) and 24 were female (48%). The median age at operation was 44 years (range 16-80). The duration of the disease before the operation was 55,5 months (range 0–242).

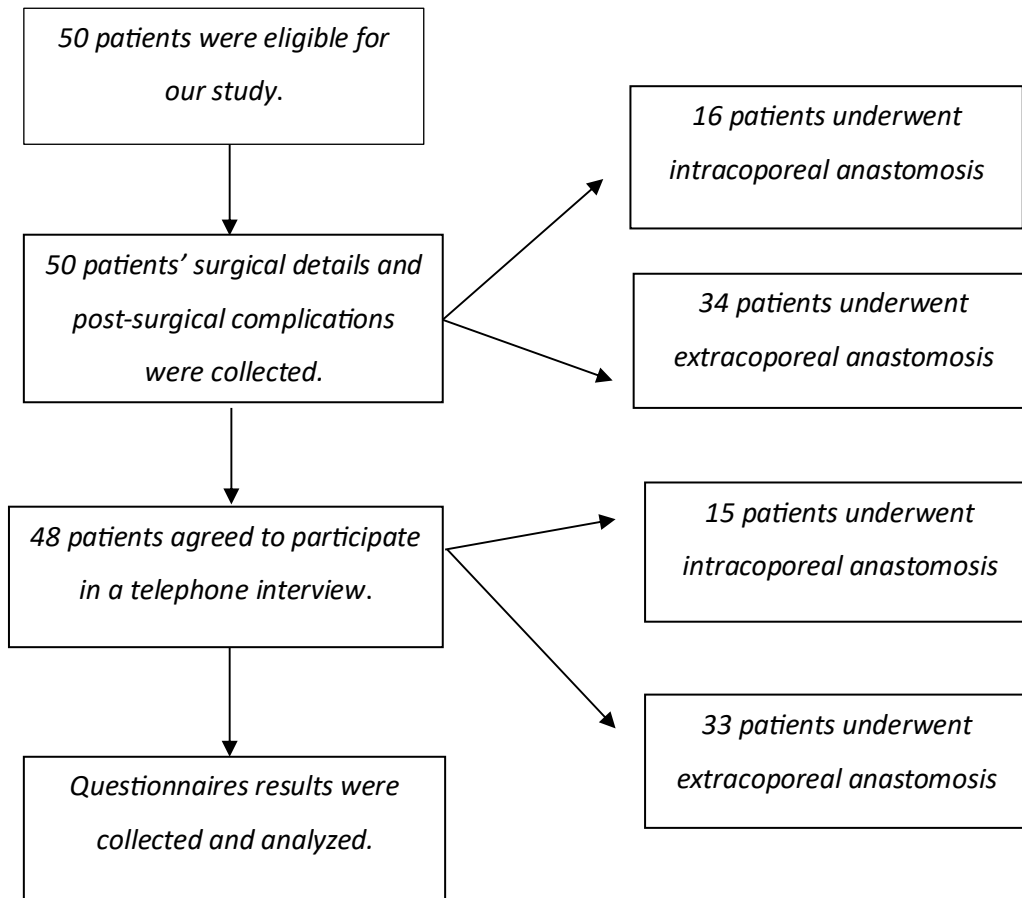
The indications for resection were a CD of the terminal ileum with critical stenosis in 44 patients (88%), of whom 7 (14%) were further complicated with abscesses and 2 (4%) had fistulas. CD involving the terminal ileum complicated by fistula or abscess without stenosis was identified in 6 patients (12%). 4 patients (8%) were diagnosed with CD affecting both the terminal ileum and the right colon; 6 patients (12%) were diagnosed with CD affecting both the terminal and middle ileum and 1 of them (2%) was also diagnosed with involvement of the jejunum; 1 patient (2%) had terminal ileum and jejunal involvement. Ileocecal resection was performed with open approach in 12 patients (24%) and with laparoscopy assistance in 38 patients (76%).

Patients were grouped according to the type of anastomosis: all 50 patients underwent side-to-side anastomosis, 16 of them (32%) received intracorporeal anastomosis and 34 (68%) received extracorporeal anastomosis. Additionally, 17 of them (34%) had stapled anastomosis and 33 (66%) had handsewn anastomosis.

The operating time was 202,5 (142-275) min for the intracorporeal anastomosis and 220 (140-375) min for the extracorporeal anastomoses. The median follow-up of the patients was 19,5 months (range 0-39).

The patients' characteristics are shown in Fig.14 and Table A.





**Fig.14** - Patients' characteristics flow-chart

**Table A - Patients' Characteristics: Preoperative, Operative, and Postoperative Predictors**

	<b>Intracorporeal anastomosis</b>	<b>Extracorporeal anastomosis</b>
<i>Demographic and past medical history</i>		
Number of patients (pts)	16 (32%)	34 (68%)
Male/Female ratio	8 (50%) / 8 (50%)	18 (52,9%) / 16 (47,1%)
Age at diagnosis (years)	24 (10-65)	39 (15-80)
Age at operation (years)	32,5 (16-70)	45,5 (19-80)
Disease duration before operation (months)	54,5 (0-181)	55,5 (3-242)
<i>Ileocolonic resection</i>		
Laparoscopy/laparotomy	16 (100%) / 0	22 (64,7%) / 12 (35,3%)
Stapled anastomosis/hand-sewn	16 (100%) / 0	1 (2,9%) / 33 (97,1%)
Operating time (min)	202,5 (142-275)	220 (140-375)
<i>Follow-up</i>		
Duration (months)	21,5 (0-36)	16,5 (3-39)
Months free from reoperation	9 (1-23)	9,5 (1-32)
CD recurrence (patients)	7 (43,8%)	11 (32,4%)
Months free from recurrence	9 (1-23)	9,5 (1-32)

*Continuous data were expressed as median (range), and categorical data were expressed as frequency and percentage.*

## 4.2 OPERATING TIME

The analysis and comparison of operative times between the two anastomosis types revealed that the median operative time for resection followed by intracorporeal anastomosis was 202.5 minutes (142-275), while for resection followed by extracorporeal anastomosis it was 220 minutes (140-375). However, there was no statistically significant difference between the two ( $p=0.1499$ ). Further analysis was conducted comparing the operating times between intracorporeal and laparoscopic extracorporeal anastomoses, excluding laparotomic patients; this revealed that the median operating time of the laparoscopic extracorporeal group was 217,5 minutes (140-265). Once again, no significant differences between the two groups were found ( $p=0,5754$ ). Operating time results are shown in Tables B and C and Fig.15.

**Table B** – Comparison between operating time of intracorporeal and extracorporeal anastomoses

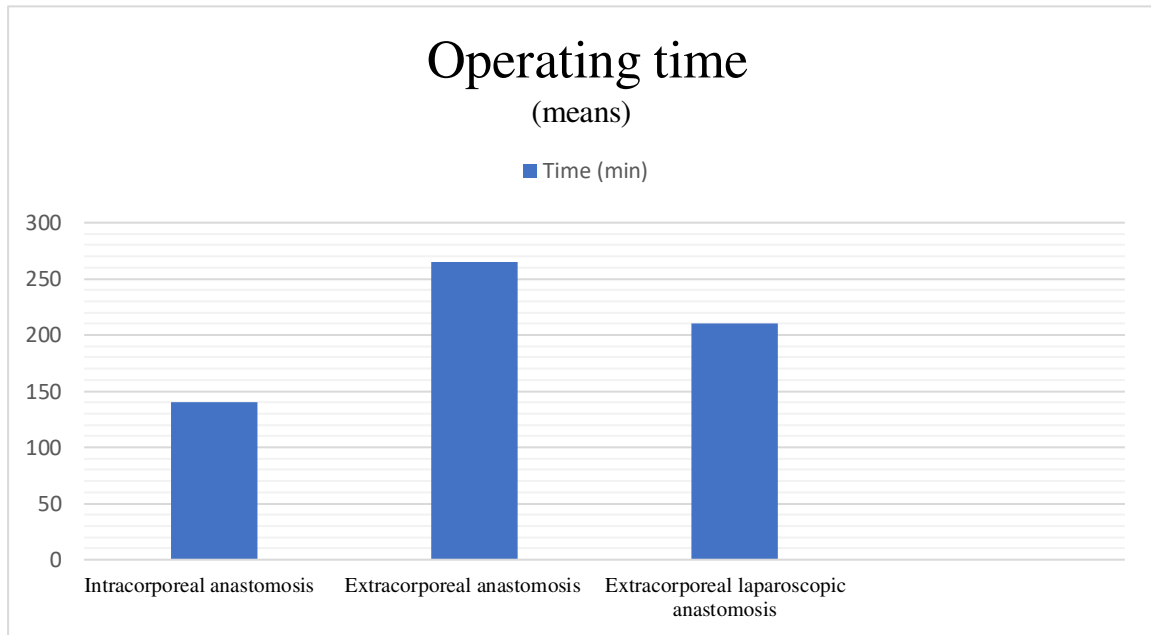
	Intracorporeal anastomosis	Extracorporeal anastomosis
Operating time (min)	202,5 (142-275)	220 (140-375)
	P= 0,1499	

*Data were expressed as median (range)*

**Table C** - Comparison between operating time of intracorporeal and laparoscopic extracorporeal anastomoses

	Intracorporeal anastomosis	Extracorporeal anastomosis (only laparoscopy)
Operating time (min)	202,5 (142-275)	217,5 (140-265)
	P= 0,5754	

*Data were expressed as median (range)*



**Figure 15.** Comparison between intracorporeal and extracorporeal anastomosis operating time. Data were expressed as means.

### 4.3 POST OPERATIVE OUTCOME

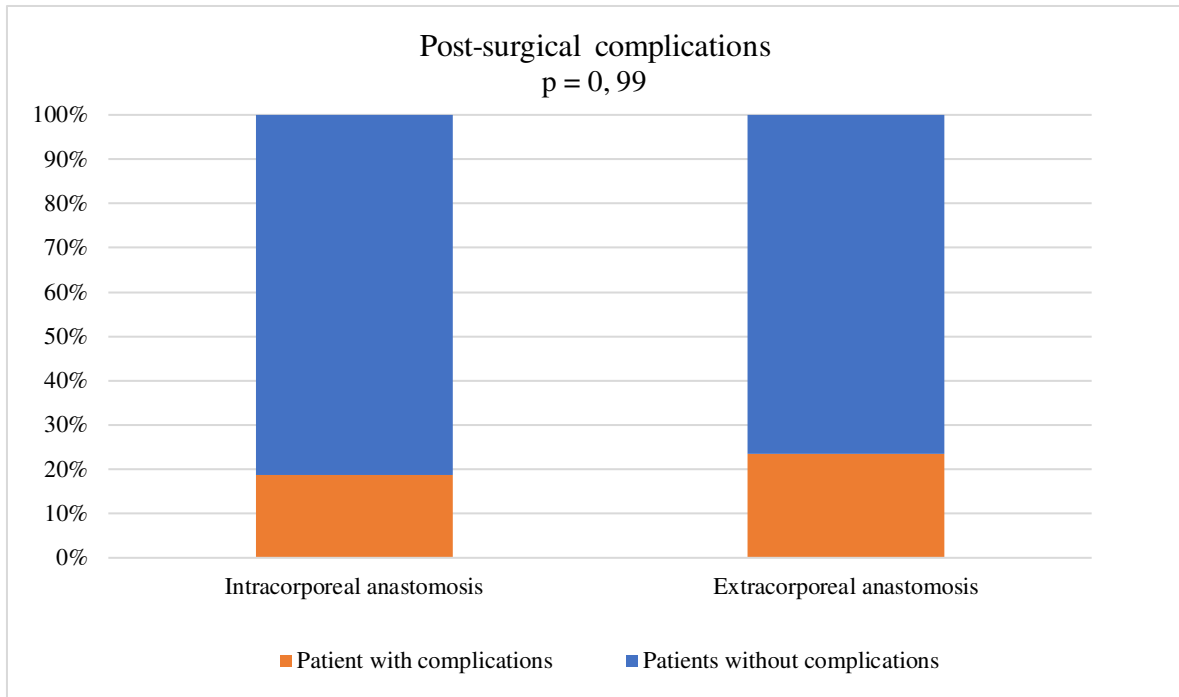
Among the 50 patients who had surgery in our department, 11 experienced postoperative complications within 30 days after surgery (22%). 8 of the patients who received an extracorporeal anastomosis (23.5%) had complications, while 3 of the patients who received an intracorporeal anastomosis (18.8%) had complications ( $p=0.99$ ). Among patients with extracorporeal anastomosis one patient (2,9%) had anastomotic bleeding (Clavien-Dindo score = 1), one (2,9%) needed hemotransfusion (Clavien-Dindo score = 2). Six (17,7%) experienced space or organ infection and were treated with antibiotics (Clavien-Dindo score = 2) and one of them (2,9%) was complicated by anastomotic dehiscence, superficial wound dehiscence, and superficial and deep wound infection and had to undergo reoperation (Clavien-Dindo score = 3b). Among the 3 patients who received intracorporeal anastomosis and experienced postoperative complications, one patient (2,9%) had space or organ infection (Clavien-Dindo score =2), and 2 (12,5%) required blood transfusions (Clavien-Dindo score =2), 1 of which (2,9%) had anastomotic bleeding (Clavien-Dindo score=2). No statistically significant differences were observed.

The list of complications is shown in Table D and Fig.16.

**Table D** – Post-surgical complications

	Intracorporeal anastomosis (n = 16)	Extracorporeal anastomosis (n = 34)	P value ( $p<0,05$ )
Anastomotic dehiscence	0	1 (2,9%)	P = 0,99
Anastomotic bleeding	1 (2,9%)	1 (2,9%)	P = 0,542
Hemotransfusion	2 (12,5%)	1 (2,9%)	P = 0,237
Superficial wound dehiscence	0	1 (2,9%)	P = 0,99
Deep wound dehiscence	0	1 (2,9%)	P = 0,99
Superficial wound infection	0	1 (2,9%)	P = 0,99
Space/organ infection	1 (2,9%)	6 (17,7%)	P = 0,65

*Data were expressed as frequency and percentage.*



**Fig.16** – Frequency (%) of post-surgical complications in patients with intracorporeal anastomosis and in patients with extracorporeal anastomosis

#### 4.4 LONG TERM OUTCOME

To assess the long-term outcome, we analyzed and compared the responses from 15 patients with CD who underwent intracorporeal anastomosis and 33 patients who underwent extracorporeal anastomosis that agreed to participate in a telephone interview.

##### *The Harvey-Bradshaw Index results*

The Harvey-Bradshaw questionnaire results did not show any significant differences in single-item or total HBI scores between the two groups. However, patients who underwent extracorporeal anastomosis had a slightly increased number of liquid/soft stools per day (HB3) than those with intracorporeal anastomosis (p = 0.077). When all items were combined to calculate the total score, patients with extracorporeal anastomosis had a slightly higher score (p = 0.0580).

Disease activity analysis revealed that 14 patients (93,3%) who underwent intracorporeal anastomosis and 25 patients (75,8%) who underwent extracorporeal anastomosis were in remission (HBI < 5).

Among those who had intracorporeal anastomosis, only one patient (6,7%) had active disease, while seven patients (21, 2%) with extracorporeal anastomosis had active disease (HBI 5-7). In addition, only one patient (3,0%) with extracorporeal anastomosis had severe disease (HBI ≥ 8). The difference between the two groups was not statistically significant (p=0.238).

The disease activity expressed with the HBI questionnaire, is shown in Tables E and F and in Fig.17 and 18.

**Table E** – HBI results.

	Intracorporeal anastomosis (n = 15)	Extracorporeal anastomosis (n = 33)	P-value (P < 0,05)
HB1	0 (0-0)	0 (0-1)	0,1634
HB2	0 (0-1)	0 (0-2)	0,5864
HB3	1 (1-4)	2 (1-7)	0,0778
HB4	0 (0-0)	0 (0-2)	0,1154
HB5	0 (0-0)	0 (0-1)	0,2253
HBTOT	1 (1-5)	2 (1-11)	0,0580

*Data were expressed as median (range)*

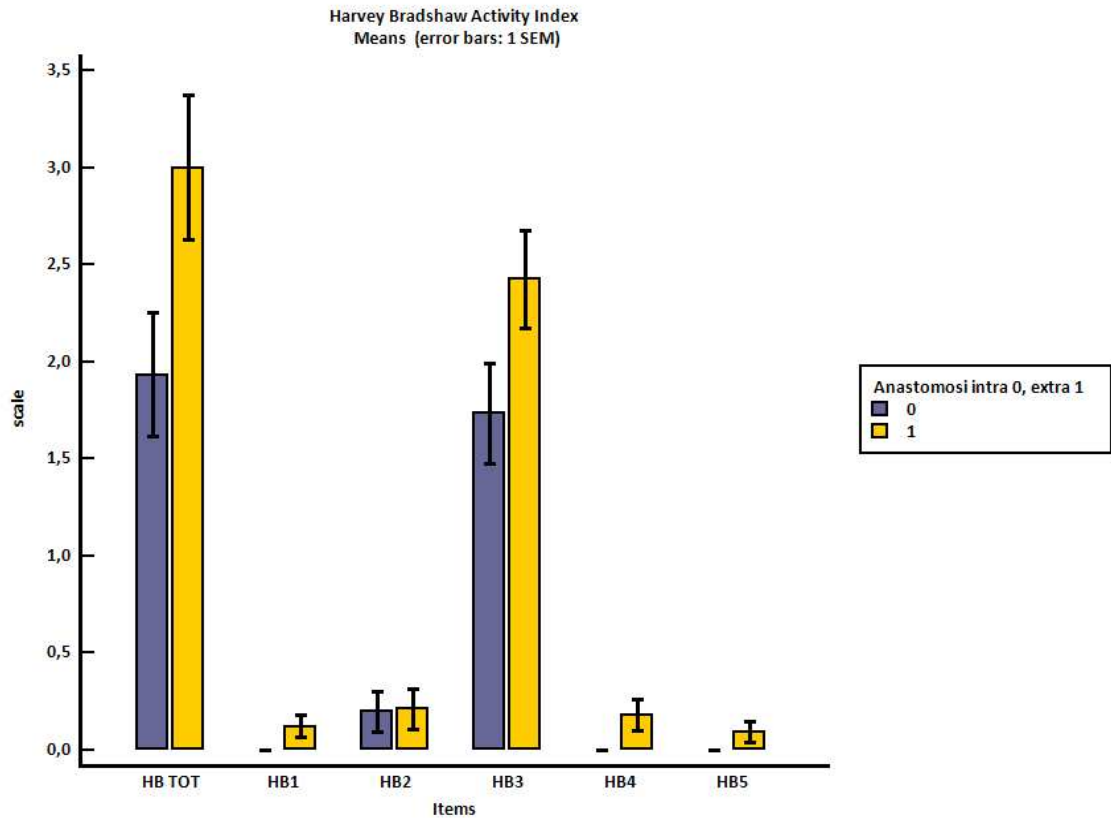


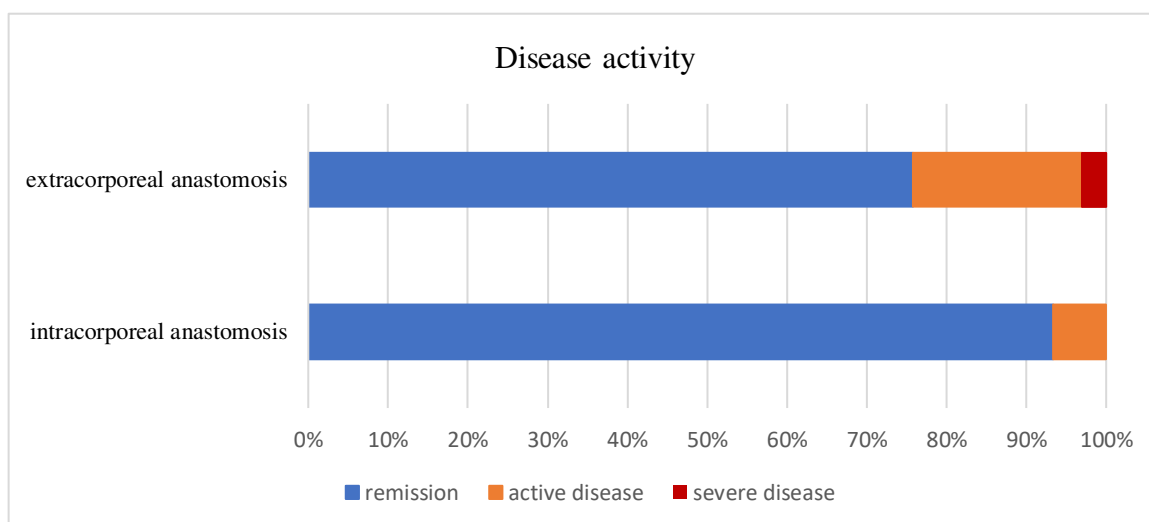
Fig. 17 - Results of HBI questionnaire

Table F – Assessment of disease activity according to the Harvey Bradshaw Index

	Intracorporeal anastomosis (n = 15)	Extracorporeal anastomosis (n = 33)	P-value (p < 0,05)
Remission (<5)	14 (93,3%)	25 (75,8%)	0,238
Active disease (5-7)	1 (6,7%)	7 (21,2%)	
Moderate/severe disease (≥8)	0	1 (3,0%)	

Data were expressed as frequency and percentage.





**Fig. 18** - Comparison between the two groups of patients' disease activity

*The Cleveland Global Quality of Life questionnaire results*

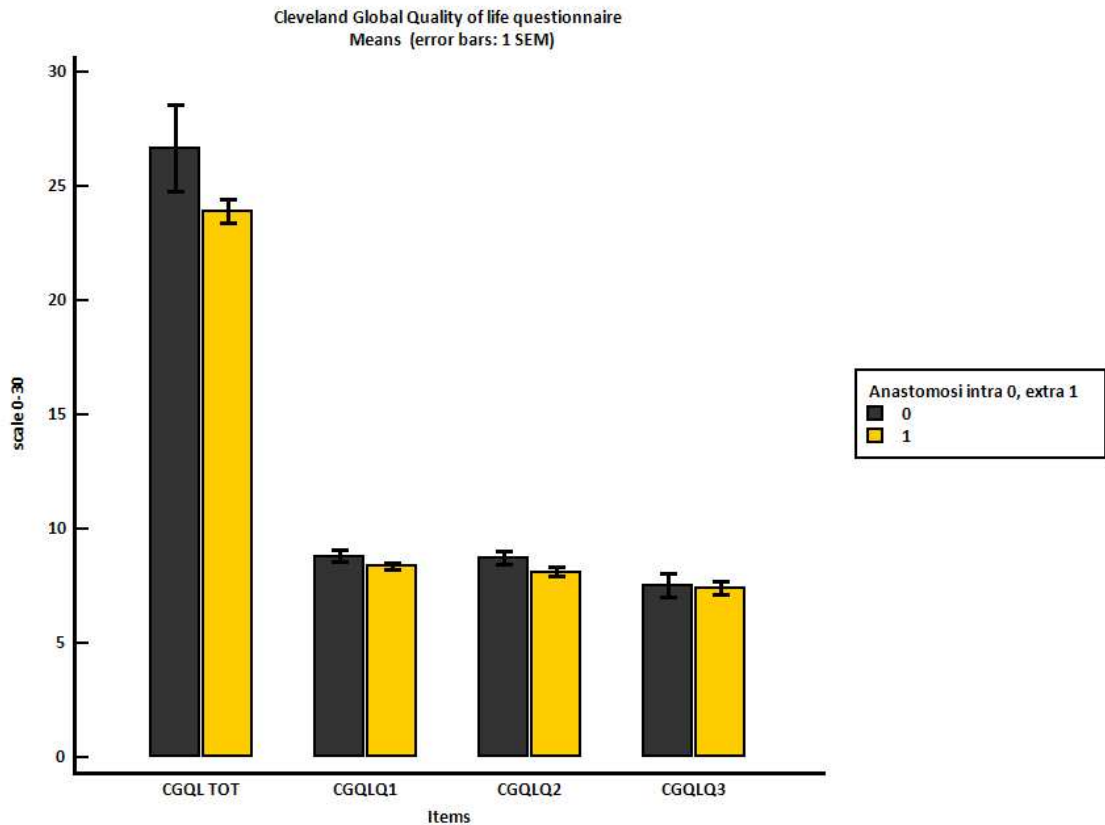
From the analysis and comparison of the CGQL questionnaire results, it is evident that there is no statistically significant difference in both patient groups.

The CGQL questionnaire results are summarized in Table G and Fig.19.

**Table G** - CGQL questionnaire results

	Intracorporeal anastomosis (n = 15)	Extracorporeal anastomosis (n = 33)	P-value (P < 0,05)
Quality of life	9 (7-10)	8 (7-10)	0,1437
Quality of health	9 (7-10)	8 (6-10)	0,0960
Energy level	8 (3-10)	8 (3-10)	0,5149
Total CGQL score	26 (17-30)	24 (17-30)	0,1331

*Data were expressed as median (range)*



*Fig. 19 - Results of CGQL questionnaire*

### *The Body Image Questionnaire results*

The results of the Body Image Questionnaire (BIQ) show that there is a statistically significant difference between the two groups for the first item (BIQ1), which asked the patients whether they were less satisfied with their bodies from the operation with a score between 1 (no, not at all) to 4 (yes, extremely). The group that received intracorporeal anastomosis was more satisfied with their bodies than the group that received extracorporeal anastomosis ( $p = 0.0270$ ).

The third item (BIQ3) asked the patients whether they felt less attractive from the operation with a score ranging from 1 (no, not at all), to 4 (yes, extremely) and the group with intracorporeal anastomosis had lower scores, indicating a higher level of satisfaction ( $p=0.0570$ ).

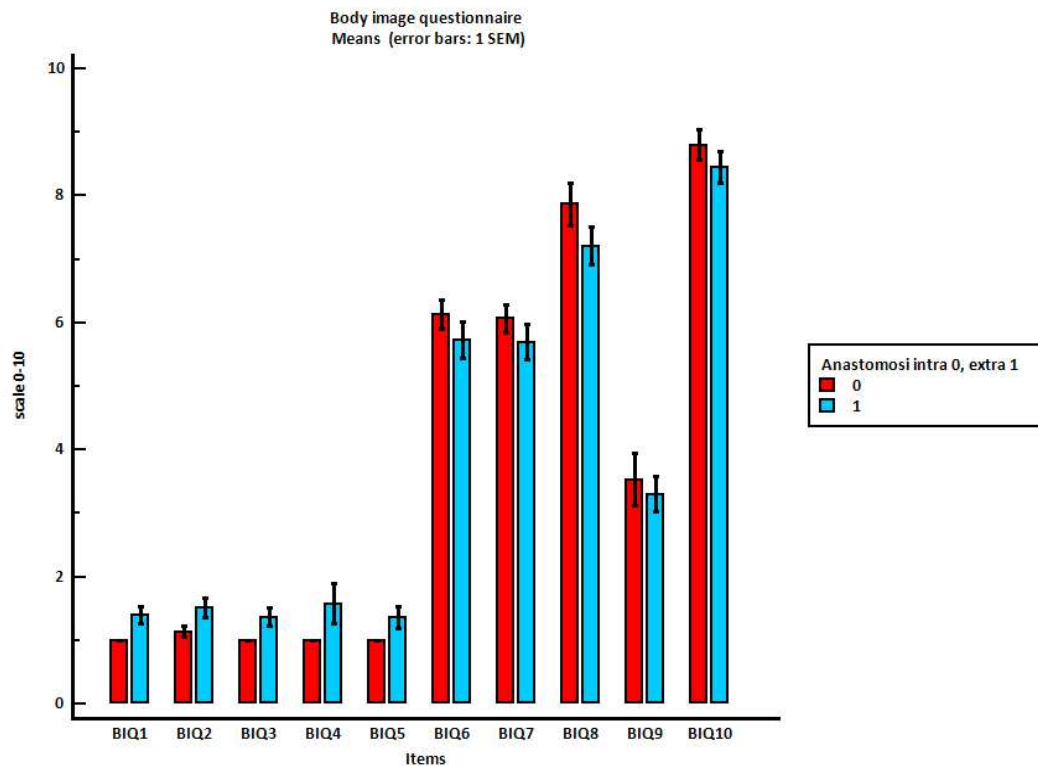
The same is true for the fourth item (BIQ4), which evaluated if they felt less feminine/masculine with a score ranging from 1(no, not at all) to 4(yes, extremely) ( $p= 0.0814$ ).

Table H and Fig.20 summarize the results of the BIQ.

**Table H - BIQ results**

	Intracorporeal anastomosis (n = 15)	Extracorporeal anastomosis (n = 33)	P value (p<0,05)
BIQ1	1 (1-1)	1 (1-4)	0,0270
BIQ2	1 (1-2)	1 (1-4)	0,1263
BIQ3	1 (1-1)	1 (1-4)	0,0570
BIQ4	1 (1-1)	1 (1-11)	0,0814
BIQ5	1 (1-1)	1 (1-5)	0,1156
BIQ6	6 (4-7)	6 (1-7)	0,7329
BIQ7	6 (4-7)	6 (1-7)	0,8242
BIQ8	8 (5-10)	8 (2-10)	0,1303
BIQ9	3 (1-7)	3 (1-7)	0,6077
BIQ10	9 (7-10)	8 (3-10)	0,4880

Data were expressed as median (range)



**Fig.20 - Results of BIQ questionnaires**

We performed additional analysis on the three questionnaires results, specifically excluding patients who underwent open surgery. The previous differences were no longer observed except for item BIQ1 which evaluated the level of satisfaction of patients' bodies. The patients who underwent laparoscopic extracorporeal anastomosis felt still less satisfied than patients who underwent laparoscopic intracorporeal anastomosis ( $p= 0,0257$ ).

#### *Clinical and surgical recurrence*

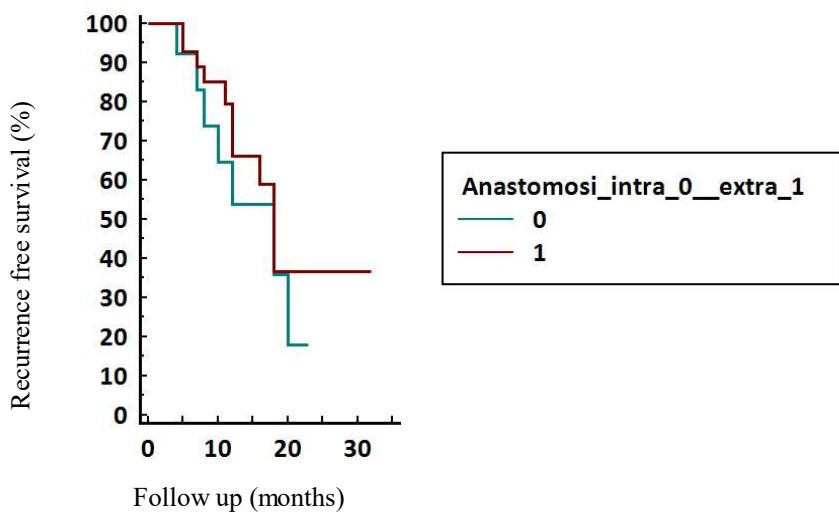
Eleven patients among those who had extracorporeal anastomosis(32,4%) and six patients among the 16 who had intracorporeal anastomosis (37,5%) experienced clinical recurrence. The median clinical recurrence-free months for patients with intracorporeal anastomosis was 9 months (1-23), whereas for patients with extracorporeal anastomosis, it was 9.5 months (1-32). However, there were no significant differences between the two groups in terms of statistical significance ( $p=0.3825$ ).

As for surgical recurrence, only one patient out of the 50 patients who underwent surgery in our department and had an intracorporeal anastomosis required reoperation due to disease recurrence. This accounts for 6.3% of all patients with intracorporeal anastomoses and 2% of the 50 patients in our study. However, this does not represent a statistically significant difference ( $p=0,169$ ).

Kaplan-Meier disease-free survival curve and reintervention free-survival curve are shown in Fig.21 and Fig.22.

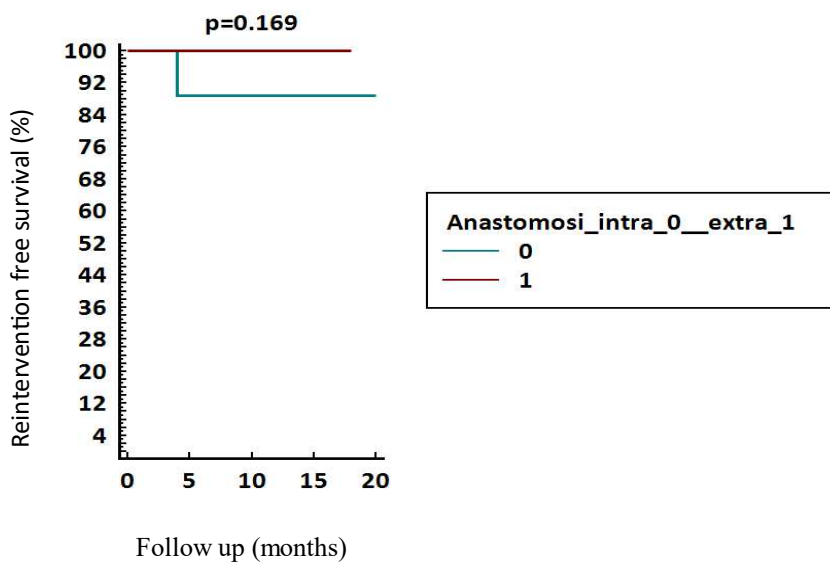
### Clinical recurrence

Significance  $P = 0,3825$   
Hazard ratio 1,4890 (95% CI 0,5548 to 4,6463)



*Fig.21 - Kaplan–Meier disease-free survival curve in the intra and extracorporeal anastomoses groups.*

### Reintervention for recurrence



*Fig.22 - Kaplan–Meier reintervention-free survival curve in the intra and extracorporeal anastomoses groups.*

## 5. DISCUSSION

Bowel resection and subsequent anastomosis to restore bowel continuity is still a widely practiced non-curative solution in patients diagnosed with Crohn's disease. Several anastomotic configurations can be used to restore bowel transit after resection, but the final decision is up to the surgeon. Important references in the literature are the ECCO guidelines, which recommend a side-to-side anastomosis and a laparoscopic approach (47).

However, no study has yet been found in the literature that analyzes the potential differences in performing the anastomosis completely intracorporeal or extracorporeal in Crohn's disease; moreover, research that compares these two anastomotic techniques has exclusively focused on colectomies for colon cancer. Therefore, our study aimed to fill this gap in the scientific literature.

We evaluated the efficacy of each method by examining postoperative outcomes, with a particular focus on any complications that occurred within 30 days of surgery including anastomotic dehiscence, anastomotic bleeding, hemotransfusion, space/organ infection, superficial or deep wound infection, and superficial wound dehiscence. The results revealed a slightly higher frequency of complications among patients with extracorporeal anastomosis, but this difference was not statistically significant.

Our findings regarding complications are consistent with several other studies in the literature, including the case-control study of Scatizzi et Al.; their study showed no differences in postoperative complications such as anastomotic dehiscence, wound infection, or surgical site infection among the 40 patients who underwent extra- and intracorporeal laparoscopic anastomosis for colon adenocarcinoma (62). These results are also consistent with the meta-analysis of randomized control trials by Creavin et Al. that reported no significant differences in anastomotic dehiscence and infection at the surgical site between the two types of anastomosis that followed neoplastic right hemicolectomy resection (63). In contrast, the study by Hellan et Al reported an increased trend of anastomosis-related complications in the extracorporeal ones. Once again, it is essential to note that outcomes were limited to patients undergoing laparoscopic right hemicolectomy for colon cancer (64).

Our study also compared the operative time between resection with intracorporeal anastomosis and resection with extracorporeal anastomosis. The results indicated a longer operative time when an extracorporeal anastomosis was performed; however, this difference was not statistically significant.

A further analysis, which excluded laparotomic surgeries, showed that there wasn't a significant difference between the intracorporeal and the laparoscopic extracorporeal anastomosis. However, a significant result was found by Anania et Al, who was able to show in his study how intracorporeal technique was faster to perform rather the laparoscopic extracorporeal one (65).

Comparing the results obtained from the Harvey-Bradshaw index at follow up, no statistically significant differences were found between the various items of the questionnaire. However, there was a tendency for patients with extracorporeal anastomosis to have a higher number of liquid stools per day, which led to an increase in the total HB score. After a more detailed examination and excluding the laparotomy patients, these differences were no longer present. To understand this, it is important to note that laparoscopic patients are likely on their first surgery, while open patients are usually on at least their second surgery and have more complex and extensive disease. Additionally, if laparotomic patients have previously undergone surgeries, their small bowel may be shorter and/or more compromised, resulting in an increased frequency of bowel evacuations.

The Harvey-Bradshaw index is a measure of disease activity. In both groups, it was observed that most patients achieved remission from the disease, a small portion had active disease, and only one extracorporeal case had severe disease. No statistically significant differences were found between the two groups.

According to the results of the CGQL questionnaire, there were no significant differences in the quality of life, health, or energy levels of the two patient groups. From the study conducted by Scarpa et Al., it was found that patients undergoing ileocolic resection for CD had CGQL scores concerning quality of life and energy levels equal to healthy patients. Only health quality levels were significantly lower between the two groups. However, this comparison does not evaluate whether an anastomosis intra- or extracorporeal was performed (66). The study by Dipasquale et Al. showed an improvement in health-related quality of life after ileocolic resection, among pediatric CD patients.

The limitations of this study are that only pediatric patients were considered and again there was no focus on the type of anastomosis performed (67).

The results from the Body Image Questionnaire (BIQ) indicate that patients with extracorporeal anastomosis are less satisfied with their bodies after the operation. They perceive themselves as less attractive and less masculine/feminine than before. This may be due to the scar resulting from the procedure. We wanted to understand if the results would be affected by the open surgery approach, which leaves a larger scar. To achieve this, we performed additional analysis of the results, specifically excluding patients who underwent open surgery. The previous differences were no longer observed except for item BIQ1 which evaluated the level of satisfaction of patients' bodies. The patients who underwent extracorporeal anastomosis were still less satisfied.

Magistro et Al. compared intracorporeal and extracorporeal anastomoses in laparoscopic colectomy for colon cancer and found out that for intracorporeal anastomosis there were better cosmetic outcomes. This result is consistent with other studies in the literature, such as the one conducted by Scatizzi et Al. (62).

In patients undergoing only laparoscopic surgery, even if the BIQ1 item indicated a significant difference between those with intra- and extracorporeal anastomosis, it is noteworthy that there were no other differences between the two groups for all the other scores obtained in the three questionnaires. This implies that the true distinction for the patient is determined by the surgical method used, whether laparoscopic or laparotomic, rather than the type of anastomosis. To support this, the study by Dunker et al. aims to assess the body image, cosmetic outcomes, and quality of life in patients with terminal ileum Crohn's disease who underwent laparoscopic-assisted or open ileocolic resection. Their findings indicate that laparoscopic surgery resulted in superior cosmetic outcomes compared to open surgery and body image correlated strongly with quality of life. But once again, it was not specified whether intra or extracorporeal anastomosis was performed (68). We believe that increasing the sample size of the study could reveal other differences that are mainly related to aesthetic outcomes.



Our analyses reveal no statistically significant differences in the risk of clinical recurrence. However, when we examined the Kaplan-Meier curves it seemed likely that intracorporeal anastomoses may result in slightly lower clinical recurrence-free survival, although we cannot confirm this statistically. Comparing surgical recurrence between the two types of anastomoses is challenging due to the limited study population and short follow-up period since our study revealed that only one patient who underwent intracorporeal anastomosis required another surgical intervention; nevertheless, there were no significant statistical differences observed between the two groups. Increasing the patient pool and extending the follow-up duration might reveal more substantial disparities and definitive findings.

### **5.1 STRENGTH POINTS OF THE STUDY**

Currently, there are no studies in the literature that have compared the postoperative outcomes of patients with Crohn's disease who underwent ileocecal resection with intracorporeal or extracorporeal ileocolic anastomosis. Thus, our study may inspire further research and studies addressing this gap in scientific literature.

### **5.2 LIMITATIONS OF THE STUDY**

The limitations of the study include a small sample size and a short follow-up period, as the time interval considered begins only in April 2020.

Future studies with longer follow-up periods and a larger study population may provide potentially significant findings.

## **6. CONCLUSIONS**

Our study shows that the intracorporeal anastomosis is slightly better than the extracorporeal in functional and aesthetic terms, although our results did not reach statistical significance. It also seems to be faster to perform and it could be related to an earlier recurrence of the disease. Regarding the post-surgical quality of life, no significant differences were found between the two types of anastomoses. There were no differences observed in postoperative complications. These results were obtained with a limited population and follow-up time and need to be verified with further studies.

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