

## ORIGINAL ARTICLE

**THE CHANGING EPIDEMIOLOGY OF CROHN DISEASE PATIENTS IN ROMANIA****L. Alecu<sup>1</sup>, I. Slavu<sup>2</sup>, A. Tulin<sup>2</sup>, S. Constantinoiu<sup>3</sup>**<sup>1</sup>General Surgery Clinic, Emergency Clinical Hospital, Agrippa Ionescu, Bucharest, Romania<sup>2</sup>General Surgery Clinic, Emergency Clinical Hospital, Bucharest, Romania<sup>3</sup>General Surgery Clinic, Sfânta Maria Clinical Hospital, Bucharest, Romania

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**Abstract**

*The landscape of Crohn disease (CD) is ever-changing. Incidence continues to vary as different population adapt to the modern western diet which consists mainly from processed foods. Our study is retrospective, data was gathered from three University Hospitals in Bucharest, Romania. To be included in the study, patients had to have a positive diagnostic of CD. The patient with CD which requires surgery in Romania is male, comes from an urban environment, is a smoker, under 50 years of age. In his case CD frequently affects the small intestine, is frequently operated in emergency settings, frequently operated for intestinal obstruction. The patient has an average duration from diagnosis to surgery of 1-3 years. The relapse free period is 2.3 years. Despite its global trend regarding the distribution of surgical interventions to those performed under elective conditions, a tendency has been observed in Romania for surgical interventions done for life-threatening complications in emergency settings. The public / patients need to be better informed about CD and its complications to seek medical help before surgery becomes mandatory.*

**Keywords:** Crohn disease, epidemiology**Introduction**

In Romania, first data offered for analysis on Crohn disease (CD) were published in 2003 by the Romanian Association of Digestive Endoscopy from 18 secondary and tertiary centers, which included a one-year analysis period between June 2002 and June 2003 and reported an incidence for CD of 0.5 / 100,000 inhabitants and a prevalence of 1.5 / 100,000, values under the European average of 5.6 / 100.000 and very low compared to the Nordic countries with the highest incidence at that time of about 8.3 / 100.000 in Sweden [1],[2].

In Romania, the trend regarding CD incidence has been increasing, so in a new epidemiological study published in 2010 an incidence of 1.09 / 100,000 inhabitants in the urban area and 0.64 / 100.000 in the rural area was reported with increased onset of new cases so the comparative prevalence between 2005 and 2009 was 69% higher [1],[2].

Surgery as a treatment method has been one of the pillars of multimodal / multidisciplinary care that a patient with CD receives [3]. The surgical treatment is largely dictated by acute complications, but as new medical treatments have become increasingly widespread and the gastroenterological surveillance has been

standardized, the influence of the surgical component has gradually been reduced.

Certain CD characteristics are associated with a higher risk for surgical complications, so it is beneficial when it is advisable to identify these patients in a timely manner according to the characteristics of the disease and extract them from the main population, so medication and surveillance are properly adopted for every individual. The present study aims to update and give contour to the epidemiologic characteristics of the surgical patient with CD in Romania. patient's diagnosed with CD undergoing surgery.

**Materials and Methods**

The study is retrospective. The period on which the data was gathered spread over 8 years (01.01.2011-01.01.2019). Data was retrieved from three Clinical Hospitals in Bucharest, Romania. The following variables were obtained: age, sex, comorbidities, the context of surgery (elective/emergency), surgical indication, preoperative medication for CD, postoperative remission, type of approach (laparoscopy/open),

A number of 62 patients underwent surgery for CD complications.

The patient population was subdivided into subgroups and compared according to the following variables: age, sex, smoking status, associated comorbidities, presence or absence of preoperative treatment, type of preoperative treatment, surgical indication, type of surgical approach (open / laparoscopic ), the context of surgery (urgency or choice), the average duration from diagnosis to surgery, the surgical indication, the type of surgery performed, the presence of relapses and their localization in the digestive tract.

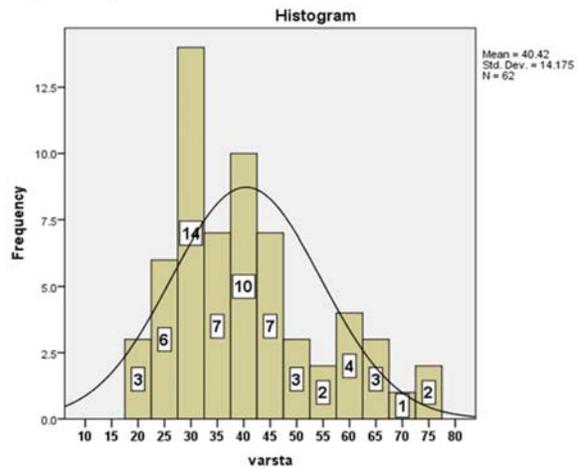
The IBM SPSS STATISTICS V20.0 program was used to perform the statistical analysis.

**Results**

A total of 62 BC patients with at least one surgical complication have been identified.

Of the total patient population, N = 27 of these were women - 43.5% and N = 35 males. The

mean age of the patient group was 40, 2 years (Figure 1).



**Figure 1 – Distribution according to age group.**

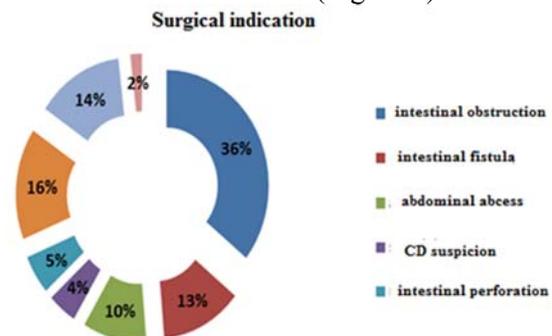
Two peaks of incidence were observed: at 20-30 years and 40-50 years (Figure 1).

Men formed the majority of the study group n = 35/62 (56%). A large number of patients were smokers, 72,6%, n=45/62.

The main co-morbidity encountered was neoplasia (n = 5), followed by cachexia (n = 4). Nodular erythema and arthralgia were found in equal distribution (n = 2) while anemia was documented in one case.

Over 50% (n = 37) of patients undergoing surgery for CD complications did not receive preoperative medical treatment, most of whom were diagnosed with life-threatening complications which required emergency surgery.

Main surgical complication which required surgery was intestinal obstruction (n = 22) followed by septic status (n = 10). Other common indications were maximum medical therapy and intestinal fistula with n = 8 (Figure 2).



**Figure 2 – Patient distribution according to surgical indication**

Open approach was used in  $n = 45/62$  patients (72.6%) while laparoscopic approach was used in the case of  $n = 13$  (21.4%).

In most of the cases, surgical intervention was performed in emergency situations:  $n = 41/62$  (66.1%) while elective surgery was done in  $n = 21/62$  (33.9%).

The most common location of CD which led to surgical complications was the small intestine  $n = 39/62$  followed by colon  $n = 24/62$  and rectum  $n = 5/62$ .

A number of  $n = 2$  patients (3.2%) experienced postoperative complications.

The average duration from diagnosis to first surgery was 2.27 years.

The surgical techniques performed were dictated by the local complications, as it follows: ileohemicolectomy  $n = 11/62$ , enterectomy and anastomosis  $N = 9/62$ , ileocecal resections  $N = 9/62$ , total colectomy  $N = 5/62$ , exploratory laparoscopy  $N = 4/62$ , abdominal abscess  $N = 4/62$ , subtotal colectomy  $N = 3/62$ , colectomy and ileostomy  $N = 3/62$ , intestinal by-pass  $N = 2/62$ , Enterectomy with colostomy and ileostomy  $N = 2/62$ , other surgery  $N = 3/62$ .

A number of 33% of the patients,  $n = 20$  suffered postoperative relapses, and  $n = 14$  required surgical reintervention with a mean duration up to 1.4 years until reintervention.

The most frequent site of relapse which required reoperation was the small intestine in 33% of cases, followed by the anastomosis in 29% of cases and colon in 19%, rectum in 14%, while perianal recurrences were observed in 5% of cases (Figure 3).

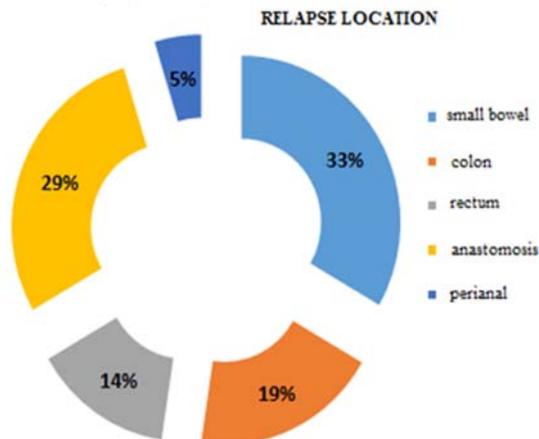


Figure 3 – Relapse location.

## Discussions

In the studied group there was a predominance of male patients and percentage was maintained in the subgroup with surgical reintervention. The genre of the patient with CD as a risk factor in postoperative relapse is still under discussion. The data in literature are contradictory, so Chardavoyne identified a higher incidence of relapse in female patients, as confirmed by Lennard et al. and Kyle J et al. [4]-[6]. However, Atwell et al. identified a higher male recurrence rate [7]. Finally, the majority of studies (Sachar DB et al; Ellis L et al; Caprilli R et al; did not offer any influence of the gender on the relapse rate [8]-[10].

Lapidus observed that the average age at diagnosis increased from 25 years in 1955 to 32 years in 1989. A bimodal peak was observed at diagnosis: 15-29 years and 55-59 years [11]. This trend was also observed in the studied group with an incidence peak of 20-30 years and a second peak at the age of 40, a trend slightly lower than the literature reports (Figure 1). This bimodal age peak at diagnosis was also confirmed by Polito et al; Card T. [12], [13].

The role of smoking in the genesis and evolution of CD is still under discussion. It is widely accepted that patients with CD are frequently smokers while smoking increases the severity of flare-up episodes simultaneously increasing their number [14]. The first observation that smoking status is associated with a higher risk of CD was made by Franceschi S. [15]. Logan in turn summarized the relative risk of being diagnosed with CD compared to non-smokers at 2.7 and 1.5 for former smokers [16]. A meta-analysis focused on 7 large studies placed the odds ratio to acquire CD with a confidence interval of 95% lifetime at 2.0 for active smokers compared to non-smokers and 1.83 for former smokers compared to non-smokers [17]. The location of CD seems to fluctuate with smoking duration and with the number of cigarettes smoked daily, so patients considered heavy-smokers (more than 10 cigarettes / day) more often have an ileo-colonic location of CD. The studied group confirms this data and strengthens the role of smoking in CD genesis - over 50% (72.6%) were smokers.

Bahler C et. has confirmed that 78% of CD patients were diagnosed with at least one

comorbidity with an average of 3 co-morbidities at the same time [18]. The most common associated pathologies encountered in these patients are rheumatologic diseases, pain, osteoporosis, neoplasia and anemia. Each combination leads to increased care costs for the health systems which care for these patients - while rheumatologic diseases and pain double their costs. In the studied group, the most common co-morbidity was cachexia followed by neoplasms and arthralgia. The presence of these extraintestinal manifestations puts in the forefront the complexity of the treatment of these patients but also the extension of CD which is not restricted to the digestive tract.

With regards to the preoperative treatment, approximately 60% of these patients did not receive medication prior to first surgery, thus drawing attention to the need to recognize these complications which require a pyramidal approach initially based on medical therapy and subsequent surgical therapy. Surgery should be kept as a last resort. However, emergency surgery still maintains high rates of use in Romania, due to acute complications (intestinal obstruction / intestinal fistula) and poor patient care at the onset of the illness - either due to lack of medical attention in time or non-compliance with lifestyle recommendations, diet or medication. Janowitz mentioned in 1974 in one of the first published articles referring to CD surgery that the patient is surgically treated for one of the major complications of CD - intestinal bleeding, obstructive syndrome or intestinal fistula, so we can observe that patients with CD have been treated since the 70's with surgery in emergency situations [19]. In the present, 50 years later, this attitude to opt for emergency surgery, begins to change. In a significant study of 30,000 patients diagnosed with CD and treated for complications published in 2011, over a period of 8 years, there had been a global reduction in the number of annual surgical interventions by 3.5%, but also an increase in elective surgery by up to 3.7% per year [18].

This trend is supported by clinical trials which have shown that early surgery in the CD - for example ileocolic locations - provide better long-term outcomes in terms of surgical relapse rate and number of hospitalizations when compared to single medical therapy [20]. Christopher M et

al. more recently in 2017 also argues the utility of elective surgery in a multicenter study [21].

On the studied population we observed that the trend regarding emergency surgery in Romania is still high - so 67% of the identified cases have been operated in an emergency setting (Figure 2). These interventions were required due to lack of response to medical therapies, but also do to delay in presentation to the physician and non-recognition of the symptomatology which predicts a flare-up.

Surgery in CD is required due to a number of local factors: intestinal obstruction, intestinal perforation, adhesions and systemic factors: sepsis or nutritional status. CD has a great heterogeneity of surgical complications which can affect any segment of the digestive tract from the oral cavity to the rectum - all this translates into a wide variety of surgical interventions making it extremely difficult to standardize surgical treatment. In these conditions observing the trends regarding the postoperative evolution of these patients as well as the surgical indications becomes difficult to obtain. In the studied group, we identified no less than 12 different surgical procedures, of which the most frequent were enterectomy with N = 9 ileostomy.

Due to the nature of CD which is systemic and involves the immune system the possibility of relapse is high so surgical interventions do not have a curative intent. The recurrence rates are high: endoscopic recurrence in the first year may reach 85% of which 10 % to 35% are clinically symptomatic. In year 3 after surgery, endoscopic recurrence is present in almost all patients and becomes symptomatic in up to 88% of cases [22]. However, Folkis et al. in a recent meta-analysis has shown that there is a difference between published studies before 1980 and after 1980 - thus a reduction in recurrence rates over time was observed - due to the increased options of medical therapies - particularly due to immunotherapy available to the patient with CD in the postoperative period [23]. Taking into account all of these facts - in the studied group the symptomatic recurrence rate was 33%, placing these values at the inferior limit of the data mentioned in the literature (Figure 3).

Although CD can affect the entire digestive tract as mentioned above, it seems that clinically symptomatic recurrences which require surgical intervention appear with a higher predisposition

to certain locations that vary according to first surgery - so if enterectomy with anastomosis was done - recurrence will most probably develop at the level of the anastomosis [24]. After colectomy with colo-colic anastomosis recurrences, tend to appear in the small intestine but in the proximal ileum [25]. The data from the present study comes to strengthen these observations as most of the recurrences were localized in the small intestine followed by the anastomosis (Figure 3).

All these data allowed the creation of an archetype of the surgical patient with CD in Romania.

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## Conclusion

The patient with CD which requires surgery in Romania is: male, comes from an urban environment, smoker, under 50 years of age, CD frequently affects the small intestine, is frequently operated in emergency settings, frequently operated for intestinal obstruction. The complications are most frequently treated with enterectomy and anastomosis. The patient has an average duration from diagnosis to surgery of 1-3 years. The relapse free period is 2.3 years.

Despite its global trend regarding the distribution of surgical interventions to those performed under elective conditions, a tendency has been observed in Romania for surgical interventions done for life-threatening complications in emergency settings. The public/patients need to be better informed about CD and its complications to seek medical help before surgery becomes mandatory.

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