*G Chir Vol. 38 - n. 6 - pp. 303-312*
*November-December 2017*

clinical practice

# Bowel perforation in Crohn's Disease: correlation between CDAI and Clavien-Dindo scores

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SUMMARY: **Bowel perforation in Crohn's Disease: correlation between CDAI and Clavien-Dindo scores.**

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Background. *Many studies have elaborated different kind of activity indices for Crohn's Disesase (CD) with the endpoint of univocally measure and evaluate the gravity of its lesions and symptoms.*

Aim. *Purpose of this work is to study and define the correlation that runs between the preoperative score obtained at the Crohn's Disease Activity Index, the occurrence of postoperative complications that will require re-intervention and the severity of the postoperative lesions evaluated using the Clavien-Dindo score.*

Patients and methods. *We have collected and analyzed data from 23 patients (12 males, 11 females) that in a period that spans from 2010 to 2016 had been recovered in our Operative Unit and then undergone surgical treatment for the perforative complications of the CD.*

Results. *The CDAI scores obtained for each patient and the data concerning their postoperative period have been analyzed using the ANOVA system. Results demonstrate the existence of a statistically signifying correlation (p = 0.0016) between the mean category's CDAI score and the Clavien-Dindo classification.*

Conclusions. *Despite the small number of patients that had been recruited and analyzed in our study, it clearly shows a statistically signifying correlation between CDAI scores higher than 150 points and the risk of occurrence of severe postoperative complications in patients that had been subjected to surgical procedures for perforative or abscessual complications in Crohn's Disease.*

KEY WORDS: Crohn - Crohn's disease - Bowel perforation - CDAI score - Clavien-dindo.

## Introduction

Crohn's Disease is a chronic inflammatory disease of the gastrointestinal tract which belongs to the family of the IBDs (Inflammatory Bowel Diseases), with others inflammatory disease as Ulcerative Colitis (UC) (which are the most frequent pathology of the group), Lynfocitic Colitis, Indeterminate Colitis (ID) and Collagenosic Colitis.

Although CD's aetiology is still unknown, it has been theorized that it might be implied a concurrence of predisposing genetic factors (12% of the patients shows familiarity for CD) (1). Environmental factors are: tobacco smoke (2), oral contraceptives (3), nonsteroidal anti-inflammatory drugs (NSAIDs) (4) and a diet poor in fibres (5); immunological factors (6-12) and infective ones (13-15).

CD's incidence varies depending on the country that's been taken in exam, but it generally shows a much larger diffusion in the western countries, probably due to the aforementioned environmental and genetic factors; furthermore, it can be observed in Europe a decreasing gradient of incidence for CD from north to south (16), with a prevalence rate that varies from 10 to 150 cases per 100.000 inhabitants. Italy currently places itself under European prevalence rates, with 7,4 and 6,5 new cases per 100.000 inhabitants every year (data refer to CD's incidence among men and women) and with the age of the disease's first appearance that follows a bimodal distribution, likewise in the other countries, with a first peak between 15 and 30 years of

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age (men showing the disease earlier in age than women) and a second peak in patients (mostly women) between 60 and 70 years old (18).

Clinically, CD is a chronic inflammatory disease that could potentially involve every point of the gastrointestinal tract (from the oral mucosa to the perianal area), but that shows a preference of localization in the small intestine (80% of the patients with CD shows signs of small intestine's involvement, especially of the terminal ileum) and of the proximal right colon (which can be the only segment interested by the disease in 25-50% of cases). It is also possible that the pathology involves both sites at the same time (50% of the cases), while the involvement of other portions of the gastrointestinal tract (such as esophagus, stomach and duodenum) is a much rarer eventuality and it's usually associated with other ileo-colic or colic lesions (19).

Due to the highly variable localization of the lesions, CD then may present itself with a rather large variety of symptoms: in fact, clinical manifestations can range from very mild to severe ones and despite the symptoms usually show a gradual progression, it is not rare that severe clinical manifestations might acutely present themselves *ab initio*. The clinical presentation of CD is also influenced by its behaviour (the pathology can show a more inflammatory, invasive or stenosing pattern) and by the general duration of the disease itself (20).

CD's diagnosis can be suspected after the patient's clinical evaluation and it can be confirmed by using a combination of instrumental and laboratory exams, as indicated by the European Crohn's and Colitis Organization (ECCO) guidelines (21, 22).

Nowadays, for the therapy of non-complicated CD, international guidelines indicate as first line treatment the medical approach only, while surgery should be taken into account only when the medical and/or target therapy can't efficiently control the symptoms anymore and patients show signs of local complications. These complications are quite common during the course of the disease and their frequency proportionally increases as CD progresses in time (from a 19% during the first year, to a 60% after 8 years from the diagnosis).

The most common local complications are: fistula (classified as entero-enteric, entero-cutaneous, entero-vescical or entero-vaginal), stenosis that can lead to sub- or frank intestinal obstruction, mild to severe intestinal bleeding, abdominal abscesses and free intestinal perforation , with consequential sepsis (24).

## Background

During the decades, many studies have elaborated different kinds of CD's activity indices for the purpose of standardizing measure to evaluate the gravity of lesions and symptoms. Those indices were used to create common guidelines that could not only help the diagnostic and therapeutic decision-making processes, but also give indications about the prognosis, the risk of relapse and the chance of success of the medical or surgical therapy.

We can distinct two different classes of evaluation indices: the endoscopic indices and the clinical ones.

The CDEIS (Crohn's Disease Endoscopic Index of Severity) (25), the SES-CD (Simple Endoscopic Score for Crohn's Disease) (26) and the Rutgeerts score (27) represent the most commonly used indices for the endoscopic evaluation of the disease's activity.

On the clinical side, which we're going to explore, we have the CDAI (Crohn's Disease Activity index) (28) which is the most used.

This index was born from the combined valuation of 8 variables, 6 of which are objective parameters such as body weight, hematocrit, number of liquid stools in the previous week, need for use of opioid antidiarrheal drugs, presence of extraintestinal complications and presence of an abdominal mass (verified by the practitioner), while the other 2 variables are subjective parameters that entirely depends on the patient's sensibility, such as the general well-being perceived in the previous seven days (rated from 0 = well to 4 = terrible) and the presence of abdominal pain in the previous week (rated from 0 = none to 3 = severe) (Table 1) (29).

As cut-off values, it's been chosen the score of 150 points for the lower limit (lower scores indicate quiescent disease) and of 450 points for the upper one (higher scores indicate a severe pathology), while an intermediate value of 220 has been arbitrarily chosen as a cut-off for the mild disease (CDAI between 150 and 220) and the moderate one (CDAI 220-450). These values can also be used during the follow-up of the medical treatment to evaluate the progression of CD: CDAI values <150 or that decreased of 70-100 points since last measurement indicate a regression of the disease, while increases of at least 70 points indicate relapse of CD (30).

Elective surgery should be considered for those patients with sub-occlusive symptoms or with CDAI over 220 (moderate disease) and ileo-colic localization: these are patients in whom medical or target

TABLE 1 - PARAMETERS FOR THE CDAI COMPILATION AND CUT-OFF VALUES (29).

| Variable | Description | Multiplier |
|---|---|---|
| Number of liquid stools | Sum of 7 days | x2 |
| Abdominal pain | Sum of 7 days rating:<br>0 = none =<br>1 mild<br>2 = moderate<br>3 = severe | x5 |
| General well-being | Sum of 7 days rating:<br>0 = generally well<br>1 = slightly under par<br>2 = poor<br>3 = very poor<br>4 = terrible | x7 |
| Extraintestinal complications | Number of complications: arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, fever >37,8 | x20 |
| Antidiarrheal drugs | Use in the previous 7 days:<br>0 = no<br>1 = yes | x30 |
| Abdominal mass | 0 = no<br>1 = questionable<br>5 = definite | x10 |
| Hematocrit | Expected – observed Hct<br>Males: 47 observed<br>Females: 42 observed | x6 |
| Body weight | Ideal/obeserved ratio<br>[1- (ideal/observed)] x 100 | x1 (NOT < -10) |

Remission: less than 150
Response: decrease greater than 70 points (100 points in more recent clinical trials)
Mild disease: 150-220
Moderate disease: 220-450
Severe disease: greater than 450

therapy struggle to keep at bay clinical manifestation and whose life quality is diminished (31-34).

Urgent surgery is requested in over 19% of patients with CD for the management of its complications, mainly pseudoappendicitis (35), intestinal occlusion, haemorrhage, megacolon, perforation and abscess.

Acute intestinal obstruction is the most frequent complication in patients with CD, especially in subjects with ileo-colic localization (35-54%), while in jejunal or colic localizations the frequency is lower (22-36% and 5-17%) (36).

Haemorrhage and toxic megacolon are much less common complications, with the haemorrhage occurring in 1-3% of patients (where the small intestine is involved in 65% of the times) (37), while the megacolon complicates 4-6% of CD's cases (38).

Intestinal perforation despite occurring in only 1-3% of patients and thus being one of the less common complication during CD's natural course, it can be the first manifestation of disease in one fourth of these patients (39). It more frequently involves the small bowel, leading to acute peritonitis which can easily degenerate in generalized peritonitis if not readily discovered (40). This complication requires urgent surgery, with abdominal toilette and bowel resection which will be aimed to spare as much intestine as possible: recent studies, in fact, have demonstrated how even if both a large and a more selective resection are effective in treating the acute syndrome, the latter is less harmful both in the present condition and in the future perspective for

the patient (41). By the light of the high recurrence rate of CD that would require further resections in the future, it would prevent the arising of a short-bowel syndrome and assure the patient a better life quality.

The resection can be completed with or without a single-step anastomosis, depending on the patient's performance status and the severity of the peritonitis: in fact, augmented levels of infectivity and inflammatory markers have been related to a poor outcome of the anastomosis, with an higher chance of leakage and further perforation (39).

Abdominal abscess, defined as an inflammatory mass originated from an intestinal perforation promptly covered by fibrin to cover the surface of the loops causing adhesions between them (42), is a complication that occurs in approximately 25% of patients. It can be associated with fistula in 40% of cases, with severe stenosis (51%) or with anastomotic recurrence (43). Presentation can range from the complaint of subacute symptoms to generalized sepsis (in 28% of patients) (44).

First line therapy for abscess consists of conservative therapy and percutaneous drainage, which gives the chance to postpone the surgical act and then to perform a resection with a one-step anastomosis. Percutaneous drainage's success varies from 65% to 96% and failures have been related to the disease's phenotype, the use of corticosteroid therapy and the presence of compartmentalized abscess (45). If the percutaneous drainage should fail, surgery is necessary with lysis of the adhesions and surgical drainage. In these patients, if the abscess is not completely or adequately drained and they are also treated with a biological immunosuppressive therapy, the risk of sepsis and anastomotic leakage would increase.

The American Society of Colon and Rectal Surgeons guidelines indicates for the surgical eradication of the abscess the resection of the involved intestine, although to avoid the resection of a too large amount of bowel and thus the future risk of a short-bowel syndrome, there's the chance to perform in urgency the drainage with a temporary ileostomy without large intestinal resections (46).

## Aim

This work aims to study and evaluate the correlation between the score of the Crohn's Disease Activity Index (CDAI) for each patient and the occurrence of postoperative complications which would request further surgical treatment and be classified using the Clavien-Dindo score.

## Patients and methods

We have collected and analyzed data of patients observed at our Operative Unit of General Surgery between 2010 (January 1st) and 2016 (December 31st) because of perforative complications of Crohn's Disease.

Patients had been selected including acute cases at admission requesting for urgent surgery due to sepsis caused by acute intestinal perforation or by abdominal abscess. We have then excluded 4 patients whose clinical records didn't have the necessary data for the compilation of the CDAI score.

In the end, 23 patients were enrolled for the study (12 males, 11 females).

We then proceeded to collect data of each patient about sex, height and age, to obtain the CDAI score (using data about weight, hematocrit, presence of abdominal mass, presence of liquid stools in the previous week, use of antidiarrheal drugs in the previous seven days, presence of extra-intestinal involvement, general well-being in the previous week and pain severity during the same period) and proceeded to evaluate the severity of the postoperative complications using the Clavien-Dindo score (Table 2) (47).

We finally divided the patients into three groups depending on the grading of their postoperative complications: CD1 patients who had not any complications or whose complications were of I grade; CD2 patients whose complications scored II grade; and CD3 patients who had postoperative complications of III grade or more severe.

## Results

For the purpose of this study 23 patients have been recruited 12 men (mean age 40,3 years) and 11 women (mean age 43,5 years) who underwent surgical percutaneous drainage (6 patients) or intestinal resection (17 patients) as a consequence of complications of Crohn's Disease.

Data obtained from these patients and their postoperative recovery have then been elaborated using the One-Way Analysis of Variance system (one-way ANOVA), and the results had shown a statistically signifying correlation ($p = 0.0016$) between the mean CDAI value for each category and

TABLE 2 - CLAVIEN-DINDO CLASSIFICATION (47).

| **Full Scale** | | | **Contracted Form** | |
|---|---|---|---|---|
| Grades | Definition | | Grades | Definition |
| **Grade I:** | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. | | **Grade I:** | Same as for full scale |
| | Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and 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 II:** | Same as for full scale |
| **Grade III:** | Requiring surgical, endoscopic or radiological intervention | | **Grade III:** | Grades IIIa & IIIb |
| **Grade III-a:** | Intervention not under general anesthesia | | | |
| **Grade III-b:** | Intervention under general anesthesia | | | |
| **Grade IV:** | Life-threatening complications (including CNS complications)‡ requiring IC/ICU-management | | **Grade IV:** | Grades IVa & IVb |
| **Grade IV-a:** | Single organ dysfunction (including dyalisis) | | | |
| **Grade IV-b:** | Multi-organ dysfunction | | | |
| **Grade V:** | Death of a patient | | **Grade V:** | Same as full scale |
| **Suffix "d":** | If the patient suffers from a complication at the time of discharge, 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, subarrachnoidal bleeding but excluding transient ischemic attacks (TIA); IC: Intermediate Care; ICU: Intensive Care Unit.

the score obtained using the Clavien-Dindo classification.

In particular, in accordance with what was reported by other studies (48), both the CD1 and CD2 groups, which had a complexive grading at the Clavier-Dindo score equal or lower than II, had mean CDAI values close to one another and both were lower than 150 points. On the other side, patients from the CD3 group who had had postoperative complications that had been graded as III or

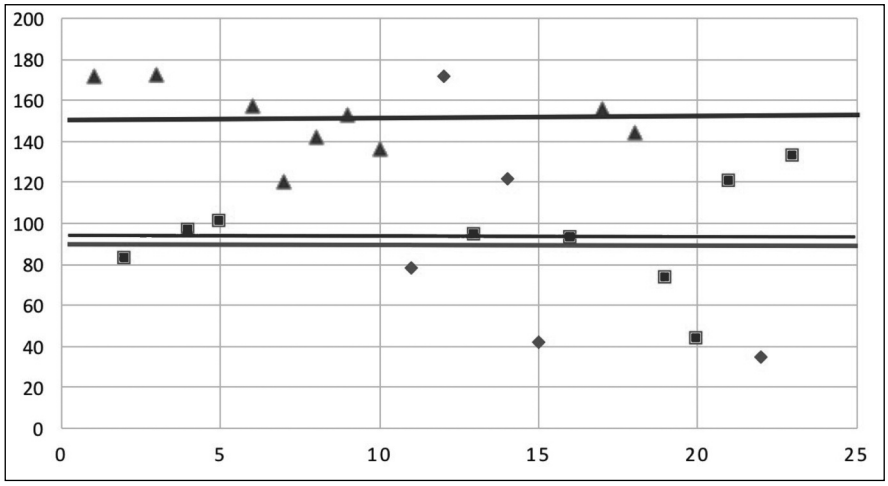


**Figure 1 - Correlation between CDAI score and groups of patients that had been divided according to their Clavier-Dindo score: ◊ = cd1 = cd2 ∅ = cd3. Both the mean CDAIs of CD1 and CD2 groups are rather close one to another and they both are under the 150 points limit; CD3 group, instead, has a mean CDAI over 150 points.**

more at the Clavier-Dindo, showed CDAI values higher than 150 points (Figure 1).

## Discussion

Using the one-way analysis of the variances (one-way ANOVA) of each group of patients (CD1, 2, 3) we have been able to demonstrate (as other studies already had) (48) a statistically signifying correlation between the CDAI score and the severity of the complications that might occur in the postoperative period.

In detail, our work had shown how complications of III grade at the Clavien-Dindo score might occur in patients with CDAI score barely higher than 150 points (esteemed cut-off: 150,33 ± 16,9) (Tables 3, 4), where other studies (48) set this kind of severe complications on a much higher cut-off (239,1 ± 52.2) (Table 5).

TABLE 4 - COMPLICATIONS OF III GRADE AT THE CLAVIEN-DINDO SCORE IN PATIENTS WITH CDAI SCORE BARELY HIGHER THAN 150 POINTS.

| | ONE-WAY ANOVA | | |
|---|---|---|---|
| | **DEVIANCE** | **GDL** | **VARIANCE** |
| SS(a) | 18806 | 2 | 9403,002 |
| SS(e) | 20824,04 | 20 | 1041,202 |
| Ss(tot) | 39630,04 | 22 | **9,030912** |
| F | | | **0,001605** |

## Conclusions

Despite the small number of patients in our study, it has clearly demonstrated the statistically signifying correlation existing between CDAI scores

TABLE 3 - COMPLICATIONS OF III GRADE AT THE CLAVIEN-DINDO SCORE IN PATIENTS WITH CDAI SCORE BARELY HIGHER THAN 150 POINTS.

| | **GROUP 1** | **GROUP 2** | **GROUP 3** | **TOTAL** |
|---|---|---|---|---|
| AVERAGE | 89,8 | 92,8974 | 150,3336 | 33,0309836 |
| S | 57,49087 | 25,78036 | 16,90495 | 41,49753196 |
| N | 5 | 59 | 9 | 23 |
| Σx | 449 | 836,0766 | 1353,002 | 2638,078852 |
| Dev | 13220,8 | 5317,016 | 2286,219 | 39630,03865 |
| Σx^2 | 53541 | 82986,35 | 205687,9 | 342215,2574 |
| (Σx)^2/N | 40320,2 | 77669,34 | 203401,7 | 321391,2224 |

higher than 150 points and the risk of occurrence of severe postoperative complications in patients that had been subjected to surgical procedures for perforative or abscessual complications in Crohn's Disease. This result not only unequivocally confirms the great importance that CDAI has both as a tool in the assessment of the inflammatory disease activity and as an accurate predictor of the possible postoperative complications, but it also opens to a whole new range of parameters (such as patient's age or inflammatory markers) that could be studied in order to evaluate their correlation with the surgical outcome and the risk of postoperative complications, and produces new tools to be used for a global evaluation of the patient and a more accurate management of the disease since its earlier stages.

TABLE 5 - RELATIONSHIPS BETWEEN THE SEVERITY OF POSTOPERATIVE COMPLICATIONS AND PREOPERATIVE PARAMETERS (48).

| | **Dindo grade 0 (*n* = 32)** | **Dindo grade II (*n* = 13)** | **Dindo grade III (*n* = 5)** | ***P* value** |
|---|---|---|---|---|
| **Age (mean ±SD)** | 40.2 ±15.8 | 34.8 ± 15.2 | 36.2 ± 12.5 | 0.548 |
| **BMI (kg/m²)** | | | | |
| **< 18.5** | 9 (52.9%) | 5 (38.5%) | 3 (17.6%) | |
| **≥ 18.5** | 23 (69.7%) | 8 (24.25) | 2 (6.1%) | 0.363 |
| **Mean ± SD** | 20.3 ± 3.4 | 19.1 ± 2.0 | 17.7 ± 2.7 | 0.14 |
| **Serum albumin (g/dl)** | | | | |
| **< 3.5** | 17 (54.8%) | 10 (32.3%) | 4 (12.9%) | |
| **≥ 3.5** | 15 (78.9%) | 3 (15.8%) | 1 (5.3%) | 0.21 |
| **Mean ± SD** | 3.32 ± 0.72 | 3.22 ± 0.56 | 3.0 ± 0.57 | 0.612 |
| **TLC (cells/mm³)** | | | | |
| **< 900** | 7 (70.0%) | 2 (20.0%) | 1 (10%) | |
| **≥ 900** | 25 (62.5%) | 11 (27.5%) | 4 (10.0%) | 0.881 |
| **Mean ± SD** | 1556.1 ± 912 | 1697.3 ± 1142.3 | 1608 ± 716 | 0.905 |
| **Preoperative systemic steroid use** | | | | 0.143 |
| **No** | 28 (70%) | 8 (20.0%) | 4 (10%) | |
| **Yes** | 4 (40%) | 5 (50%) | 1 (10%) | |
| **Operation type** | | | | 0.662 |
| **Emergency** | 11 (73.3%) | 3 (20.0%) | 1 (6.7%) | |
| **Elective operation** | 21 (60%) | 10 (28.6%) | 4 (11.4%) | |
| **Extent of operation** | | | | 0.061 |
| **Small bowel resection** | 13 (86.7%) | 1 (6.7%) | 1 (6.7%) | |
| **RHC** | 17 (60.7%) | 9 (32.1%) | 2 (7.1%) | |
| **Combined** | 2 (28.6%) | 3 (42.9%) | 2 (28.6%) | |
| **Operation method** | | | | 0.082 |
| **Laparoscopy** | 10 (62.5%) | 6 (37.5%) | 0 | |
| **Open** | 22 (64.7%) | 7 (20.6%) | 5 (14.7%) | |
| **POSSUM score** | | | | |
| **Physiological subscore** | 17.9 ± 3.8 | 18.4 ± 3.4 | 18.4 ± 4.7 | 0.931 |

*to be continued*

Continued from Table 5

| | | | | |
|---|---|---|---|---|
| **Operative subscore** | 11.1 ±4.1 | 12.1 ± 3.2 | 14.0 ± 9.8 | 0.413 |
| **Estimated morbidity** | 0.31 ± 0.2 | 0.36 ± 0.2 | 0.43 ± 0.4 | 0.524 |
| **Estimated mortality** | 0.06 ± 0.05 | 0.08 ± 0.07 | 0.17 ± 0.2 | 0.049 |
| **CDAI score** | | | | |
| **< 150** | 7 (100%) | 0 | 0 | |
| **≥ 150** | 25 (58.1%) | 13 (30.2%) | 5 (11.6%) | 0.032 |
| **Mean ± SD** | 190.1 ± 49.6 | 218.1 ± 41.2 | 239.1 ± 52.2 | 0.048 |
| **SNUBH-NST** | | | | |
| **Normal** | 21 (63.6%) | 9 (27.3%) | 3 (9.1%) | |
| **At risk of malnutrition** | 11 (64.7%) | 4 (23-5%) | 2 (11.8%) | 0.932 |
| **ICU stay (days)** | 1.25 ± 0.9 | 1.31 ± 0.7 | 3.8 ± 2.1 | < 0.001 |
| **Diet start (postoperative day)** | 5.2 ± 1.6 | 4.7 ± 0.9 | 9.6 ± 3.1 | < 0.001 |
| **Hospital stay (days)** | 10.47 ±4.1 | 12.9 ±9.1 | 25.2 ±19.9 | 0.002 |

BMI: Body Mass Index; TLC: Total Lymphocyte Count; RHC: Right HemiColectomy; POSSUM: Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; CDAI: Crohn's Disease Activity Index; SNUBH-NST: Seoul National University Bundang Hospital Nutritional Screening Tool; ICU: Intensive Care Unit.

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