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Alimentary Tract

Earlier surgery is associated to reduced postoperative morbidity in ileocaecal Crohn's disease: Results from SURGICROHN – LATAM study

SURGICAL IBD LATAM CONSORTIUM

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ABSTRACT

Background: Early surgical resection is an emerging concept for patients with ileocaecal Crohn's disease (CD). The aim of this study was to compare postoperative outcomes after ileocaecal resections between patients with luminal and complicated CD.

Methods: A retrospective analysis of patients operated for ileocaecal CD during an 8-year period in ten tertiary referral academic centres from Latin America was performed. Patients were allocated into 2 groups: those operated for early (luminal) disease (Early Crohn's Disease -ECD-) and for complications of CD (Complicated Crohn's disease -CCD-). A comparative analysis was performed regarding short-term outcomes of surgery, considering overall postoperative complications as main outcome.

Results: 337 patients were included in the analysis, 60 (17.80%) in the ECD group. Smoking and exposure to perioperative biologic drugs were more prevalent in CCD group. CCD patients had increased requirement of urgent surgery (26.71 vs. 15%, $p = 0.056$), longer operative time (164.25 vs. 90.53 min, $p < 0.01$), lower rates of primary anastomosis (90.23 vs. 100%, $p = 0.012$), increased rate of overall postoperative complications (33.21 vs. 16.67%, $p = 0.013$), more reoperations (13.36 vs. 3.33%, $p = 0.026$), and higher rates of major anastomotic fistulas and hospital stay. On multivariable analysis, smoking ($p = 0.001$,95%CI: 2.59–32.11), operative time ($p = 0.022$,95%CI:1–1.02), associated procedures ($p = 0.036$,95%CI:1.09–15.72) and intraoperative complications ($p = 0.021$,95%CI:1.45–92.31) were independently related to presenting postoperative complications.

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Conclusion: Early (luminal) ileocaecal resections were associated to lower rates of overall postoperative complications. Proper timing for surgery, avoiding delays in surgical indication can impact postoperative outcomes.

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1. Introduction

Crohn's disease (CD) is a chronic, inflammatory entity which can affect any part of the gastrointestinal tract. The ileocaecal region is the most affected segment, in up to 2/3 of patients [1]. Traditionally, for patients with localized ileocaecal CD, medical treatment with biological drugs has been considered the standard of care after patients fail to conventional treatment [2], leaving indication of surgery for patients who develop failure to optimized medical therapy or complications of the disease (stenotic or penetrating CD) [3]. However, resections for complicated CD, with already established bowel damage, are usually delayed, and patients usually end up having surgery in a poor general condition, which can affect postoperative outcomes [4,5].

For this reason, some publications, mostly based on the prospective LIR!C trial, have suggested that an early resection (in patients with inflammatory luminal component, without stenotic or penetrating complications) comprises a reasonable choice in localized ileocaecal CD [6,7]. Based on these studies, some centres have started operating ileocecal CD in an earlier fashion, but results of these strategy compared to patients operated for complicated disease are still scarce in literature.

Our study aimed to perform a retrospective comparative analysis between patients submitted to ileocaecal resection for luminal disease (earlier in the disease course) and complicated CD (with stenotic or penetrating complications), with major focus in overall postoperative complications between the groups.

2. Materials and methods

2.1. Ethical considerations

The study was approved by Institutional review boards from all included centres, according to good clinical practice standards.

2.2. Study design and setting

Ten inflammatory bowel disease (IBD) specialized, academic tertiary centres from four Latin American countries (Argentina, Brazil, Chile and Colombia) were invited to participate in this study.

The participating centres were selected due to their experience in the management of IBD patients, and all of them receive referrals from lower volume centres in their respective countries, with an internal multidisciplinary team to discuss CD surgical cases.

2.3. Inclusion criteria

Adult patients submitted to primary resections for localized ileocaecal CD (affection of the last 40 cm. of terminal ileum and/or cecum) during 2012–2020 in the participating centres were included in this retrospective study.

Exclusion criteria were previous CD-related abdominal surgery and presence of CD activity in other intestinal segments (non-localized ileocaecal CD).

3. Data collection and management

A retrospective review of eligible patients' clinical registry was done by each center. The information related to patients' comorbidities and operative procedures were collected in an electronic database designed for this purpose.

The database was reviewed for face validity by three experts in colorectal surgery and biostatistics to identify key issues and to maximize completeness and accuracy. The lead investigator checked the accuracy of all cases to ensure data quality. When missing data was identified, the local lead investigator was contacted and asked to complete the record. Afterwards, the record was accepted into the dataset for analysis. Those individuals whose information could not be completely retrieved were not included in the study.

Patients were allocated into 2 groups:

a) Early (luminal) surgery (*Early Crohn's Disease* – ECD): Patients operated for uncomplicated (luminal) inflammatory disease. ECD was defined according to Maruyama et al. [8]: resection performed for inflammatory disease with purely luminal involvement, without previous resections (not related to postoperative recurrences, with no fibrotic stenosis or internal or external fistulas or blocked perforation).
b) Late (complicated) surgery (*Complicated Crohn's Disease* – CCD): Patients operated for associated complications of CD (fibrotic stenosis or penetrating phenotype) in the ileocaecal region.

Patients with luminal disease, suitable for surgery, were those who had persistently active CD limited to ileocecal region and failed to respond to conventional treatment (steroids or immunomodulators), or to any line of biologics. In these patients, full mapping of the disease including high-resolution CT or MRI was performed, and CD-related complications such as stenosis or fistulas were ruled out (which would make surgical treatment mandatory). Subsequently, in patients with exclusive luminal component, induction with biologicals or surgical resection was chosen on an individual basis, including multidisciplinary and patients' decisions.

3.1. Variables analyzed

Information regarding comorbidities and previous exposure to medical treatment was gathered to identify possible differences between the groups.

Preoperative variables: Charlson comorbidity score, smoking (at the moment of surgery), body mass index (BMI), presence of preoperative anemia, preoperative albumin levels, ASA score and history of previous abdominal procedures.

Disease-related variables: time from diagnosis of CD to surgery, Montreal classification of CD, preoperative exposure to biological agents within 12 weeks of surgery, perianal disease, previous use of corticosteroids (defined as having received more than 20 mg/day of prednisolone or equivalent for up to 6 weeks before surgery) [9], and requirement of preoperative nutritional optimization before the procedure (defined as patients who needed to be hospitalized in order to receive enteral or parenteral nutrition before undergoing surgery).

Intraoperative variables: Operative time, character of the procedure (elective or emergency), operative approach and conversion rate, intraoperative complications (stratified according to CLASSIC Classification) [10], associated procedures (defined as an additional CD-related procedure other than the resection of the compromised bowel at the ileocecal region) and performance of primary anastomosis.

Postoperative variables: length of hospital stay, presence and characterization of complications according to Clavien-Dindo classification [11], anastomotic leak rate (stratification based on the International Study Group for Rectal Cancer classification) [12], readmission and reoperation rates, as well as mortality within 30 days of the procedure.

3.2. Outcomes

Primary outcome was to compare overall postoperative complication rates between the ECD and CCD groups. Our secondary outcomes were to compare preoperative, intraoperative, and additional postoperative characteristics between the groups.

3.3. Statistical analysis

The software Stata (Statistical data analysis) was used for the analyses (v11.1, Statacorp, College Station, Texas USA). Categorical variables were described as percentages whereas numerical variables were described as median and range. The normality of each numerical variable was evaluated visually and with the Kolmogorov Smirnov test. We used the chi square test and Fisher's exact test (when appropriate) for the comparison of categorical variables and the Student T test for quantitative variables. Odds Ratio (OR) with 95% CI were additionally calculated. A multivariable analysis using a multivariable logistic regression model was performed including all the variables compared with a p value of less than 0.05 or considered clinically significant by authors.

A p value below 0.05 was considered statistically significant.

4. Results

A total of 337 patients with primary ileocecal Crohn's disease were included in the study, 60 (17.8%) in the ECD and 277 (82.2%) in the CCD groups, respectively.

4.1. Preoperative characteristics

Information related to preoperative variables in both groups are described in detail in table 1. The groups were considered homogeneous regarding age, concomitant or previous hypertension or dyslipidemia, Charlson comorbidity index, ASA score, previous abdominal surgery, or other comorbidities. On the other hand, smoking was more prevalent in the CCD group (22.38 vs. 8.33%, $p = 0.013$, OR: 3.17). Patients in this group were also more exposed to biologicals within 12 weeks from the surgical procedure (68.97% vs. 42.86%, $p = 0.006$, OR: 2.96), despite the overall prevalence of exposure to biological agents at any time of disease course prior to surgery was not statistically different between both groups. Time from CD diagnosis to surgery was longer in the CCD group (66.81 vs. 47.40 months, $p = 0.065$). There were no differences between the groups regarding rates of preoperative anemia, preoperative albumin levels or requirements of nutritional optimization preoperatively. Additionally, no differences in BMI (24.00 vs. 22.79, $p = 0.457$) or in previous use of corticosteroids at the time of surgery (39.71 vs. 30.00, $p = 0.187$) were observed.

4.2. Intraoperative variables

Most of the parameters used to evaluate intraoperative and postoperative results were different between early and complicated surgery groups (table 2). Length of surgical procedure (operative time) was significantly longer in complicated patients (164.25 vs. 90.53 min, $p = < 0.001$), who also had a lower rate of primary anastomosis (90.25 vs. 100%, $p = 0.012$). Requirement of an associated procedure was also more frequent in this group (17.69 vs. 6.67%, $p = 0.033$, OR: 3.24). The most performed additional procedures were segmental small bowel resection (20.41%), segmental sigmoid resection (20.41%) and sigmoid primary closure (10.20%), secondary to ileo-sigmoid fistulas.

ECD patients had numerically lower rates of intraoperative complications, yet this result was not statistically significant. Initial laparoscopic approach was similar in both groups, but the conversion rate to laparotomy was also numerically higher in CCD patients, despite not statistically significant. The main reasons for conversion in the complicated group were the presence of an inflammatory mass (47.06%), followed by invasion of target organs (23.53%) and intraoperative bleeding (5.88%).

4.3. Postoperative results

Length of hospitalization was longer in complicated patients (8.33 vs. 6.48 days, $p = 0.208$). Overall complications were higher in CCD patients (33.21 vs. 16.67%, $p = 0.013$, OR: 2.49). The rate of major complications (Clavien-Dindo > IIIa) in the ECD group was 40% as compared to 51.09% in CCD patients ($p = 0.548$). Despite not significant, rates of anastomotic leakage were numerically higher in the complicated group (6.67 vs. 1.67%, $p = 0.173$). These data are illustrated in Fig. 1. Furthermore, the only patient that presented a fistula in the ECD group did not require a reoperation, whereas almost all leakages in the CCD cohort required additional surgical procedures.

Lastly, CCD patients had significantly more reoperations (13.36 vs. 3.33%, $p = 0.026$, OR: 4.47), but no differences were found in readmissions or mortality between the groups.

4.4. Multivariate analysis

Table 3 describes in detail the results of multivariate analysis using overall postoperative complications as a dependent variable. Smoking ($p = 0.001$, 95%CI: 2.59–32.11), operative time ($p = 0.022$, 95%CI:1–1.02), associated procedures ($p = 0.036$, 95%CI:1.09–15.72) and intraoperative complications ($p = 0.021$, 95%CI:1.45–92.31) were independently related to presenting postoperative complications.

5. Discussion

This international Latin American study of postoperative complications in CD patients submitted to ileocaecal resections demonstrated that patients with earlier surgery in the disease course (performed in the presence of uncomplicated luminal disease) presented lower overall postoperative complications as compared to patients operated for complicated disease (stenotic or penetrating phenotypes).

In the present study, differences in surgical outcomes between groups were notable. Patients operated earlier had significantly shorter operative time, less urgent procedures, lower rates of postoperative complications and less reoperations. Furthermore, they had less requirements of CD-related associated procedures and were more likely to receive a primary anastomosis (and, consequently, avoid stomas). Kotze et al. described surgical outcomes in patients submitted to elective resections in CD with less or

Table 1
Preoperative variables.

Variables	All patients (*N* = 337) (100%)	ECD (*N* = 60) (17.8%)	CCD (*N* = 277) (82.2%)	P value
Sex, female (n,%)	177 (52.52)	36 (60)	141 (50.90)	0.201
Age (median, range)	39.78 (18 - 89)	38.13 (19 - 89)	40.14 (18 - 83)	0.380
Smoking	67 (19.88)	5 (8.33)	62 (22.38)	**0.013**
BMI (median, range)	22.87 (14 - 37)	24.00 (18 – 30.1)	22.79 (14 - 37)	0.457
Hypertension	25 (7.42)	4 (6.67)	21 (7.58)	0.806
Dyslipidemia	11 (3.26)	1 (1.67)	10 (3.61)	0.442
Charlson comorbidity score (median, range)	0.60 (0 - 8)	0.42 (0 - 4)	0.63 (0 - 8)	0.195
Anemia	67 (19.88)	11 (18.33)	56 (20.22)	0.740
Other comorbidities	30 (8.90)	5 (8.33)	25 (9.03)	0.865
Previous abdominal surgery	81 (24.04)	12 (20.00)	69 (24.91)	0.420
Time from diagnosis to surgery (months, median, range)	63.36 (0 - 504)	47.40 (0 - 240)	66.81 (0 - 504)	0.065
Emergency surgical procedure	83 (24.63)	9 (15.00)	74 (26.71)	0.056
Montreal classification				
A1	21 (6.23)	4 (6.67)	17 (6.14)	0.878
A2	235 (69.73)	41 (68.33)	194 (70.04)	0.795
A3	81 (24.04)	15 (25)	66 (23.83)	0.847
B2		N/A	155 (55.96)	
B3		N/A	101 (36.46)	
B2–3		N/A	21 (7.58)	
Previous perianal disease	93 (27.60)	15 (25.00)	78 (28.16)	0.750
Previous exposure to steroids	128 (37.98)	18 (30.00)	110 (39.71)	0.187
Previous exposure to biologics	180 (53.41)	35 (58.33)	145 (52.35)	0.476
Previous complications associated to biologics	23 (12.78)	5 (14.29)	19 (12.41)	0.766
Exposure to biologics within 12 weeks before surgery	115 (63.89)	15 (42.86)	100 (68.97)	**0.006**
Requirement of preoperative nutritional optimization	50 (14.84)	12 (20.00)	38 (13.72)	0.215
Albumin level (median, range)	3.48 (1.2 – 5.2)	3.40 (1.3 – 4.79)	3.49 (1.2 – 5.2)	0.548
ASA				
I	62 (18.40)	15 (25)	47 (16.97)	0.145
II	239 (70.92)	42 (70)	197 (71.12)	0.863
III	34 (10.09)	2 (3.33)	32 (11.55)	0.055
IV	2 (0.59)	1 (1.67)	1 (0.36)	0.233

Table 2
Operative results.

Variables	All patients (*N* = 337) (100%)	ETCD (*N* = 60) (17.8%)	CTCD (*N* = 277) (82.2%)	P value	OR (95% CI)
Operating time (median, range)	151.43 (45–420)	90.53 (45 - 180)	164.25 (85 - 420)	**< 0.005**	
Laparoscopic approach	173 (51.34)	29 (48.33)	144 (51.99)	0.608	1.16 (0.66–2.03)
Conversion rate	18/173 (10.40)	1/29 (3.45)	17/144 (11.81)	0.179	3.75 (0.47–29.84)
Requirement of associated procedures	53 (15.73)	4 (6.67)	49 (17.69)	**0.033**	3.24 (1.23–8.53)
Intraoperative complications	22 (6.53)	1 (1.67)	21 (7.58)	0.093	4.84 (0.63–37.13)
CLASSIC Minor	19/22 (86.36)	1/1 (100)	18/21 (85.71)	0.684	N/A
CLASSIC Major	3/22 (13.64)	0	3/21 (14.29)	0.684	N/A
Primary anastomosis	310 (91.99)	60 (100)	250 (90.25)	**0.012**	< 0.001
Hospitalization days (median, range)	8.03 (2 – 81)	6.48 (2–48)	8.33 (2 – 81)	0.208	N/A
Postoperative complications	102 (30.27)	10 (16.67)	92 (33.21)	**0.013**	2.49 (1.19–5.17)
Minor complications (Clavien – Dindo < IIIa)	51/102 (50)	6/10 (60)	45/42 (48.91)	0.505	0.64 (0.17–2.43)
Major complications (Clavien - Dindo > IIIa)	51/102 (50)	4/10 (40)	47/92 (51.09)	0.548	1.62 (0.43–6.15)
Clavien - Dindo					
I	15/102 (14.71)	2/10 (20)	13/92 (14.13)	0.619	0.66 (0.12–3.49)
II	36/102 (35.29)	4/ 10 (40)	32/92 (34.78)	0.743	0.80 (0.21–3.07)
IIIa	11/102 (10.78)	2/10 (20)	9/92 (9.78)	0.323	0.43 (0.08–2.40)
IIIb	25/102 (24.51)	1/10 (10)	23/92 (25)	0.288	3.31 (0.40–28.14)
IVa	11/102 (10.78)	1/10 (10)	10/92 (10.87)	0.933	1.10 (0.12–9.70)
IVb	0	0	0		
V	4/102 (3.92)	0	4.35 (4/92)	0.501	
Anastomotic leak	16/310 (5.16)	1/60 (1.67)	15/250 (6.00)	0.173	3.77 (0.48–29.36)
Minor leak	2 (12.50)	100 (1/1)	1/15 (6.67)	0.006	
Major leak	14/16 (87.50)	0	14/15 (93.33)	0.006	
Readmission to hospital	30 (8.90)	4 (6.67)	26 (9.39)	0.502	1.45 (0.49–4.33)
Reoperation	39 (11.57)	2 (3.33)	37 (13.36)	0.026	4.47 (1.03–19.33)
Mortality	4 (1.19)	0	4 (1.44)	0.349	

more than 5 years of disease duration (time from diagnosis to surgery). Their findings demonstrated that patients with more than 5 years from diagnosis had higher rates of overall surgical complications ($p = 0.011$), reoperations ($p = 0.003$), surgical site infections ($p = 0.014$), anastomotic dehiscences ($p = 0.021$), abdominal abscesses ($p = 0.021$), and overall medical complications ($p = 0.019$). In their study, on logistic regression, the single significant variable linked to increased complications was the confection of stomas (OR: 3.203; 95%CI: 1.011–10.151; $p = 0.048$). An important difference from the study from Kotze et al. and the present analysis is that in their sample, small bowel resections were included, and only elective procedures were considered. Thus, if these findings can be transposed to ileocaecal resections in general, this still needs more evidence.

Despite the main findings of our study seem expected, comparison of our results with previously published studies seems chal-

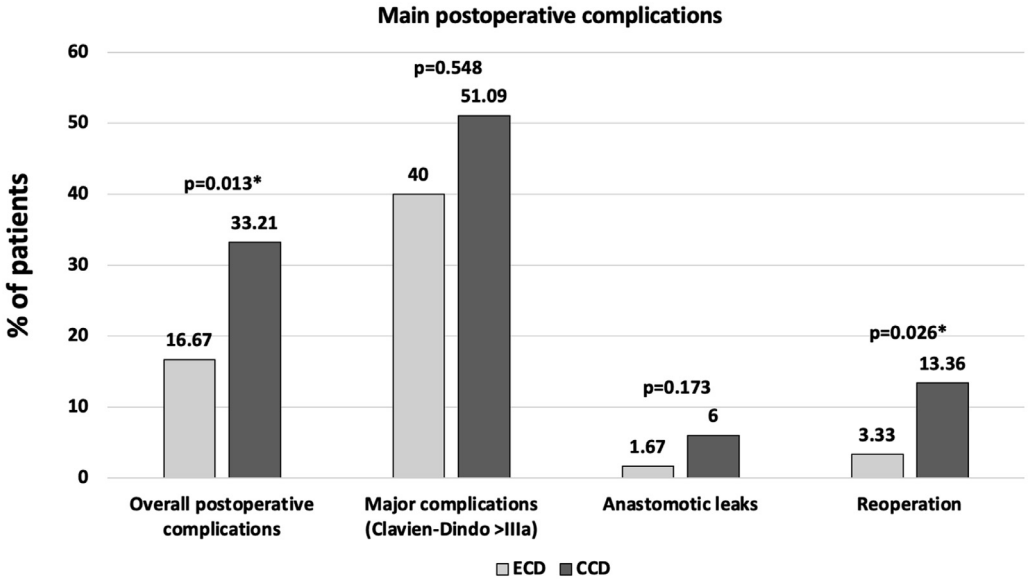

Fig. 1. Main postoperative outcomes between the groups.

Table 3
Multivariate analysis considering overall complication rate as dependent variable.

Variable	OR	Standard Error	P value	95% CI
Smoking	9.14	7.859	0.001	2.59 – 32.11
Time from diagnosis to surgery	0.99	0.004	0.830	0.99 - 1.01
Emergency procedure	1.85	1.46	0.438	0.39 – 8.73
Surgery for CD complications	8.20	10.25	0.092	0.71 – 94.91
Exposure to biologicals within 12 weeks of surgery	0.38	0.237	0.122	0.109 – 1.296
Operative time	1.01	0.005	0.022	1.00 – 1.02
Associated surgical procedure	4.15	2.820	0.036	1.09 – 15.72
Intraoperative complications	11.56	12.252	0.021	1.45 – 92.31
Primary Anastomosis	0.33	0.250	0.144	0.07 – 1.47

lenging, as publications that compare surgery for luminal versus complicated ileocecal CD are scarce. The LIR!C study [6,7] was the first prospective study to propose early surgery as an alternative to biological agents for second line treatment of ileocecal luminal disease. It compared surgery with infliximab, and demonstrated that ileocaecal resections in luminal disease presented durable remission, and comprise an alternative to biological therapy in this specific phenotype of CD. In LIR!C, the postoperative rate of major complications (Clavien-Dindo > IIIa) was similar to what was observed in our study in the ECD group (6.67%). The rate of anastomotic leaks in that study, on the other hand, was higher (4%) than in ECD patients in our study (1.67%). An important point to be emphasized is that LIR!C only included laparoscopic ileocaecal resections, differently from our multicentric study, which had the majority of patients operated with conventional approach. Furthermore, the main outcome of LIR!C was also different (quality of life after 12 months, and not postoperative morbidity).

After LIR!C, other groups have compared earlier and delayed surgery using different definitions, mostly based on time from diagnosis of CD to surgery [5,13-15]. It is important to understand that time *per se* may not be the single variable involved in this comparison. Complications of the disease (such as fibrotic stenoses or internal/external fistulas) can occur in different time intervals, in different patients. This means that a patient with an internal fistula, for example, can develop this complication and be operated before one year of diagnosis, and patients with luminal disease avoid surgery for longer periods. This suggests that the complicated phenotypes of CD are more important than time (as a single variable) in relation to more complicated procedures and higher rates of postoperative morbidity. Even though none of these studies can be compared with our cohort, since group definitions were different, earlier surgery in CD course presented lower morbidity and better postoperative outcomes than CD-related ileocaecal resections for complications of the disease [16–18]. On the other hand, major complications after resections for luminal disease seem to be lower, as demonstrated in the LIR!C trial and in our study. It is also important to emphasize that postoperative morbidity can be increased not only by disease-specific factors in complicated CD, but also in management and patients' conditions preoperatively, despite no differences in the study groups were identified to this extent.

One of the secondary outcomes of our study was to compare preoperative characteristics between the groups. The only significant different variable between patients with luminal and complicated CD was the previous exposure to biological therapy, more prevalent in complicated patients. However, in multivariate analysis, this was not associated to higher morbidity. Both groups were homogeneous regarding comorbidities, BMI, preoperative anemia, or hypoalbuminemia at the time of surgery. Furthermore, there was no significant difference between groups regarding previous exposure to steroids at the time of surgery. Lastly, no difference was identified in requirements of preoperative nutritional optimization (patients requiring hospitalization for parenteral or enteral nutrition before surgery). In the European Society of Coloproctology (ESCP) snapshot study in CD ileocaecal resections ($n = 375$), preoperative parenteral nutrition was associated to worse postoperative outcomes (OR 2.36, 95% CI 1.10–4.97) [19]. This was not observed in our study.

Our study is associated with some limitations, which need to be considered. The retrospective study design and the multicentric characteristic may have impacted our results and can potentially be associated to a selection bias. Intrinsic differences between centres may also account for additional bias, as surgical practices may vary in terms of surgical indications, mostly between the countries. We also analyzed data from a convenience sample, and no statistical power calculation was performed, what could cause type I errors due to limited numbers in different variables. Another limitation is the proposed definition of early resection not being based in time, but in luminal disease and absence of complications. There is no consensus in the literature regarding this classification. In the absence of a validated classification, this seems a more real definition to be used in clinical practice, as the development of complications may vary in an individual basis, not only based in time. Lastly, some of the variables found to be independently related to overall postoperative complications in the multivariable analysis (smoking, associated procedure and intraoperative complications) presented a large 95% IC range, suggesting that these results should be interpreted with caution.

Despite these limitations, our study has strengths. Groups were homogeneous regarding most preoperative variables and the number of patients operated earlier in the disease course with luminal disease was considerable ($n = 60$). This is also the first study ever to show outcomes of IBD surgery at a regional scale in Latin America, and also the first to describe in detail outcomes of ileocecal resections for CD, which may serve as a guide to definition of proper timing regarding surgical indication in multidisciplinary decisions in the continent.

In summary, ileocaecal resections performed earlier in the disease course, in luminal phenotype, were associated to reduced overall postoperative morbidity in comparison to resections for complicated CD, associated to fibrotic stenosis or penetrating complications.

Our findings suggest that special attention should be given to patients with ileocaecal CD who are refractory to medical therapy. Delays in surgical indication may be associated to the development of intrinsic complications of the disease, which are associated to unfavorable postoperative outcomes. More publications are needed aiming to a more precise definition of early or late surgery for primary ileocaecal Crohn's disease. Indications for surgery need to be discussed in multidisciplinary teams with individualization of therapeutic strategies to each patient, positioning earlier surgical resection as an important option even before biologics for selected patients in the management of ileocaecal CD.

Further studies should focus on comparison of long-term results between these two groups, regarding time to relapse and management of those relapses.

Declaration of Competing Interest

All the authors have no conflict of interest and this project was not funded.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.09.011.

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