Surg. Gastroenterol. Oncol. 2024;29(2):112-120 DOI: 10.21614/sgo-678

Predictors of Long-Term Clinical Response in Complex Perianal Fistulizing Crohn's Disease - A Retrospective Study

Ana Cristina Silva[1,2]*, Ezequiel Silva[1,2], Pedro Brandão[1,2], Mónica Sampaio[1,2], Andreia Teixeira[4,5,6], Paula Lago[3], Marisa Domingues Santos[1,2]

***Corresponding author:**
Ana Cristina Ferreira da Silva Madureira Ana Cristina Silva, MD
Colorectal Unit, General Surgery Service Santo Antonio Local Health Unit, Largo Prof. Abel Salazar, 4099-001, Porto, Portugal
Ciкncia ID: 781F-F2FE-093E; ORCID iD: 0000-0002-0345-0432
E-mail: u07035@chporto.min-saude.pt

[1]Colorectal Unit, General Surgery Service, Santo Antonio Local Health Unit, Porto, Portugal
[2]School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal
[3]Gastroenterology Service, Santo Antonio Local Health Unit, Porto, Portugal
[4]MEDCIDS - Department of Community Medicine, Information and Decision in Health Faculty of Medicine, University of Porto, Porto, Portugal
[5]CINTESIS@RISE - Centre for Health Technology and Services Research Faculty of Medicine, University of Porto, Porto, Portugal
[6]ADiT-LAB, Polytechnic Institute of Viana do Castelo, Nun'Alvares Industrial and Commercial School Street, Viana do Castelo, Portugal

Abbreviations:
CD: Crohn's Disease;
IBD: Inflammatory bowel disease;
PF: Perianal fistulas;
EUA: Examination under anesthesia;
3D-EAUS: Three-dimensional endoanal ultrasonography;
pMRI: Pelvic magnetic resonance imaging;
Anti-TNFα: Anti-Tumor necrosis factor alfa;
cPF: Complex perianal fistulas;
ECCO: European Crohn's and Colitis Organisation;
IFX: Infliximab;
ADA: Adalimumab;
MSCs: Mesenchymal stem cells;
SALHU: Santo Antonio Local Health Unit;
"1st surgery": 1st surgery in our institution;
EIMs: Extraintestinal manifestations;
AGA: American Gastroenterological Association;
EO: External openings;
M: Mean;
sd: Standard deviation;
Min: Minimum (min);
Max: Maximum;
Med: Median;
Q1: first quartiles;
Q3: third quartiles;
A: Age;
L: Location;
B: Behaviour;
OR: Odds ratio;
CI: Confidence intervals.

Received: 20.04.2024
Accepted: 15.06.2024

ABSTRACT

Background: Treatment of complex perianal fistula (cPF) in Crohn's Disease (CD) constitutes a major challenge for gastroenterologists and surgeons. The aim of this study is to review the experience of a tertiary reference centre and identify prognostic factors related to non-response to treatment.
Methods: Retrospective cohort study of adult patients with CD operated on for cPF, in a tertiary reference centre, from January 2015 to June 2023 and followed up until December 2023. Characteristics of patients, of CD and of cPF, and clinical response to treatment were collected from electronic medical records. Logistic regression models were applied to identify variables associated with nonresponse and clinical recurrence.
Results: Seventy-nine patients were included (50.6% male) with a median follow-up of 85 months (interquartile range, 37-124); all of them were discussed by the multidisciplinary team. At time of 1st surgery in a tertiary referral centre, cPF were transsphincteric in 53.2% patients, suprasphincteric in 22.8% and rectovaginal in 15.2%. In 88.6% of patients the first procedure was seton placement. All but 2 patients were treated with 1 to 4 biologic drugs. At end of follow-up, a complete or partial response was achieved in 78.5% patients and 21.5% had nonresponse or a recurrence. Due to perineal destruction 3 patients required an ostomy and other 3 a proctectomy.
Conclusion: Complete or partial response to combined biologic and surgical treatment was achieved in 78.5% of patients. Suprasphincteric fistula was a risk factor and female sex was a protective one for worse outcomes of Crohn's cPF. A multidisciplinary group approach, the identification of long-term response factors and the emergence of new therapeutic weapons can improve treatment results.
Key words: Crohn´s disease, perianal fistula, surgery, biologics, treatment outcome

INTRODUCTION

Incidence of Crohn's Disease (CD) has been increasing in recent decades in

Western and developed countries (1). Crohn's Disease is a chronic inflammatory bowel disease (IBD), with transmural involvement that can occur in any area of the digestive tract, from the mouth to the anus. It is an incurable and heterogeneous disease with different presentations, behavior and prognosis [Montreal Classification (2)]. The aim of treatment is to control inflammation to avoid complications and tecidular structural damage.

Perianal disease (PD) appears in about one third of CD patients, presenting as the dominant complain in 5% of them (3,4). It is related with more aggressive behaviour (5) and worse quality of life with risk of multiple abscesses, destruction of sphincters and perineum, neoplasia and protectomy. It is essential to classify Crohn´s perianal fistulas (PF) and to identify predictors of long-term clinical response for a correct therapeutic approach (6). Perianal fistula tracts morphology, activity of disease and abscess presence are accessed by clinical evaluation, including examination under anesthesia (EUA), which can be best complemented by three-dimensional endoanal ultrasonography (3D-EAUS) and/or pelvic magnetic resonance imaging (pMRI). Crohn´s PD treatment is a major challenge, requiring discussion in a Multidisciplinary IBD Team, and combined medical and surgical treatment to increase response rates and thus prevent or minimize complications (5).

Anti-tumor necrosis factor alfa (Anti-TNFα) treatement is the most effective pharmacological approach to induce and maintain complete or partial response of complex perianal fistulas (cPF). The European Crohn's and Colitis Organisation (ECCO) Guidelines recommend infliximab (IFX) as the first pharmacological choice combined with surgical intervention (7-9). Nevertheless, adalimumab (ADA) may play a role in patients in whom optimized therapy with IFX has failed due to immunogenicity and/or a low serologic level of drug. Although more studies are needed, ustekinumab and vedolizumab may be effective in Anti-TNFα refractory individuals (9,10).

There is insufficient evidence for the use of immunomodulator drugs (tiopurines or Methotrexate) alone or in combination with biologic terapy to induce and maintain remission of cPF (9,10). Corticosteroids have no place in the treatment of perineal Crohn's disease. Antibiotics can be used, alone or concomitant with other treatment, in presence of perianal abscesses (9,10).

Surgery should focus on drainage of abscesses and seton placement to control infection before and during biologic treatment associated or not with other sphincter-preserving procedures, as indicated (8). Other surgical options are advancement flap, ligation of the intersphincteric fistula tract, laser, and fibrin glue, with clinical remission rates of 61%, 47 to 95%, 69% and 38%, respectively (8,11). Fistulotomy or fistulectomy is an option for complex low fistulas (5). Anal fistula plug should not be routinely considered for the closure of PF in Crohn's disease (9). Mesenchymal stem cells (MSCs) therapy is a recent, safe, and promising therapeutic option, with 51.5% and 56.3% combined remission rate at 24 weeks and 52 weeks posttreatment, respectively (12). Preferably it should be used in absence of proctitis (12).

About 6% patients may require major surgery, as last therapeutic option. Patients with irreversive structural damage, uncontrolled symptoms, refractory to treatment, severe proctitis and neoplasia may require protectomy (13). Derivative stoma may be indicated in presence of severe perineal sepsis or in patients who initially refuse proctectomy proposal (8).

The aim of this study is to review experience with patients treated at a tertiary reference centre for cPF secondary to CD and identify variables that may influence clinical response under a combined pharmacologic and surgical approach.

MATERIALS AND METHODS

Study population

Retrospective study of a cohort of consecutive patients with cPF secondary to CD who underwent ≥1 cPF surgery in a tertiary reference centre, between January 2015 and June 2023 and followed up to December 2023. All patients were discussed in a Multidisciplinary IBD Team involving Gastroenterologists, Surgeons, and Radiologists.

Inclusion criteria: CD patients aged ≥18 years operated for cPF at Colorrectal Surgery Unit of Santo António Local Health Unit (SALHU) with or without previous surgery in other institutions.

Exclusion criteria: PF due to other etiologies such as cryptoglandular, iatrogenic (post-surgical), malignancy, radiotherapy, human immunodeficiency vírus and trauma obstetric or other.

Data of patients were collected from electronic medical records and stored in a SPSS v.27 database, according to a previously designed protocol. This study was approved by the institutional Ethics Committee, and data were collected respecting patient anonymity at all stages.

Data collection included the following variables:

1) Patient sex and age at diagnosis of CD; 2) Patients data at time of 1st surgery in SALHU (referred as "1st surgery" hereafter): age, smoking status and familial IBD), disease duration, Montreal classification (2), extraintestinal manifestations (EIMs), clinical assessment of cPFs according to American Gastroenterological Association classification (AGA) (14) and Parks Classification (15), number of external openings (EO), concomitant perianal disease, related injuries and proctitis); 3) Previous medical and surgical treatment in the "1st surgery" and in subsequent ones; 4) Follow-up results at last appointment. Statistical analysis was performed to identify prognostic factors related to treatment response.

Study design

According to the AGA classification, PF may be simple or complex. High intersphincteric, high transsphincteric, suprasphincteric and extrasphincteric fistulas are complexes (15), as are those with multiple tracts and multiple external openings (EO), and those associated with abscesses, anorectal stenosis, with active anal and/or rectal CD and with rectovaginal fistulas (14).

Before surgery and at follow-up, patient´s PF was assessed only by clinical and endoscopic examination as not all patients were evaluated by imaging means. Preoperative EUA was routinely performed and first postoperative evaluation within a month after each surgery.

Biologic treatment at the "1st surgery" was defined by their onset up to at least 6 months before surgery, and by its maintenance or onset within 3 months after surgery.

Classification of response

Treatment response definitions from Present et al (16) were applied. Complete clinical response (clinical remission) was defined as the absence of any draining fistula at two consecutive visits at least 4 weeks apart. Clinical response was defined as partial if there was a ≥50% reduction in drainage in two visits with a minimum interval of 4 weeks. Clinical nonresponse was defined by the maintenance of draining fistula(s) and clinical recurrence by the reappearance of a draining fistula(s) at any time after complete response.

Statistical analysis

Data analysis was performed using SPSS v.27. Categorical variables were described by absolute and relative frequencies, n (%). Normally distributed continuous variables were summarized by mean and standard deviation, M (sd). Non-normally distributed continuous variables were summarized by minimum (min) and maximum (max) values, median and interquartile range, Med (Q1; Q3), with Q1 and Q3 being the first and third quartiles, respectively.

To find out which variables were associated with worse outcome - nonresponse and /or clinical recurrence - simple and multiple logistic regressions were performed. Significant variables at 20% in the simple models were included in an initial multiple model. Subsequently, they were eliminated, one by one, in decreasing order of p-value, until a final model was obtained, with only significant variables at 5%. The results of these regressions were presented using the odds ratio (OR), respective 95% confidence intervals (95% CI) and the respective p-value. The adequability of the final model was evaluated using the Hosmer & Lemeshow test.

RESULTS

The studied included a cohort of 79 consecutive patients with a male:female ratio of 1:0.98, and a median age of 28 years (Q1=21 and Q3=38). At time of CD diagnosis, the Montreal Age classification was A1 – n=6 patients (7.6%), A2 – n=59 (74.7%); and A3 – n=14 (17.7%) (table 1). Crohn´s disease has been diagnosed 0 to 144 months (median 24 months) previously to "1st surgery": n= 35 ≤1 year (44.3%), n= 25 >1 and <10 years (31.6%), and n=19 ≥10 years (24.1%). The first clinical manifestation of CD was intestinal and perianal in 50 patients (63.3%) and in 9 (11.4%) the perineal complaints were the dominant ones. Extraintestinal manifestations appeared at any time in 26 patients (32.9%) with predominance of musculoskeletal and mucocutaneous diseases, present in 15 and 12 patients respectively.

At the time of the "1st PF surgery" median age of patients was 36 years old (Q1=26 and Q3 =47). Twenty-seven patients (34.2%) were smokers and 11 (13.9%) had family history of IBD. According to Montreal Classification (2), most of them were L3 (40.5%) and B1 (58.2%) (*table 1*).

As shown at *table 2*, at time of "1st surgery" the main symptoms of patients were perianal pain and/or purulent discharge. From the 79 patients, 39 (49.4%) had one fistula tract and about a quarter had a horseshoe-shaped tract (25.3%). Forty-two patients (53.2%) had transsphincteric PF, 18 suprasphincteric

Table 1 – Characteristics of 79 patients with Crohn's disease and complex perineal fistula at the 1st surgery in a tertiary referral centre ("1st surgery")

Variables	years (Q1- Q3)[a]
Median age at diagnosis	28 (21-38)
Median age at "1st surgery"	36 (26-47)
Sex	n pts[b] (%)
Male	40 (50.6)
Female	39 (49.4)
Duration of CD (years)	
≤ 1	35 (44.3)
>1 and ≤ 10	25 (31.6)
>10	19 (24.1)
Smoking status	
Non-smoker	40 (50.6)
Ex-smoker	12 (15.2)
Current Smoker	27 (34.2)
Montreal Classification	
Age[c]	
A1	6 (7.6)
A2	59 (74.7)
A3	14 (17.7)
Location [d]	
L1	20 (25.3)
L2	13 (16.5)
L3	32 (40.5)
L1+L4	9 (11.4)
L2+L4	1 (1.3)
L3+L4	4 (5.1)
Behavior [e]	
B1	46 (58.2)
B2	20 (25.3)
B3	13 (16.5)

[a]Q1 and Q3: first and third quartile; [b]pts:patients; Montreal Classification [c]Age (yrs) – A1: <17; A2: 17–40; A3: >40; [d]Location – L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper disease, [e]Behavior - B1: nonstricturing, nonpenetrating, B2: structuring, B3: penetrating (2)

Table 2 – Clinical characteristics of Crohn's complex perineal fistula at the time of "1st surgery" [a] in the 79 patients

Clinical characteristics	n pts [b] (%)
Symptoms	
Perianal pain / swelling	49 (62.0)
Anoperineal discharge / suppuration / bleeding	68 (86.1)
Vaginal discharge / suppuration	4 (5.1)
Fecal urgency / incontinence	2 (2.5)
PF classification [c]	
High Intersphincteric	32 (40.5)
High Transsphincteric	42 (53.2)
Extrasphincteric	2 (2.5)
Suprasphincteric	18 (22.8)
Ano/rectovaginal	12 (15.2)
Number of EO [d]	
0 [e]	18 (22.8)
1	39 (49.4)
2 ou 3	20 (25.3)
≥ 4	2 (2.5)
Concomitant perianal disease and related injuries	
None	27 (34.2)
Abscess	25 (31.6)
Fissure	16 (20.3)
Proctitis	31(39.2)
Anorectal stricture	6 (7.6)
Anal ulcer	5 (6.3)

[a] "1st surgery": 1st surgery at Santo António Local Health Unit (SALHU); [b] pts: patients; [c] PF classification: Parks Classification of Perianal fistulas; [d] EO: external openings; [e] Abscesses without external openings

Table 3 – Surgical procedures in the 79 Crohn´s patients with complex perineal fistula: previously operated [a], at "1st surgery"[b] and subsequently

Type of procedures	n
Previous Surgery [a]	
Abscess drainage	38
Fistulotomy or fistulectomy	11
Seton placement	8
Internal lateral sphincterotomy	3
Laser	2
Hemorrhoidectomy	1
"1st Surgery" [b]	
Seton placement	54
Seton placement with abscess drainage	16
Fistulotomy or fistulectomy with abscess drainage	9
Subsequent Surgery	
Seton placement	95
Abscess drainage	37
Fistulotomy or fistulectomy	5
Laser	5
Protectomy	3
Stoma	3
MSCs [c] therapy	2
LIFT [d]	1

[a] In other institutions; [b] "1st surgery": 1st surgery at SALHU; [c] MSCs: Mesenchymal stem cells; [d] LIFT: ligation of intersphincteric of fistula tract

(22.8%) and 12 (15.2%) had rectovaginal fistula. In addition to cPF, abscesses were the second main presentaton. Furthermore, it should be noted that 31 patients (39.2%) patients had proctitis and 6 (7.6%) had sphincter injuries.

Forty-five (47.0%) from the 79 patients had previous PF surgery, 17 (21.5%) of whom had two or more operations (*table 3*). The two procedures most adopted in "1st surgery" was the placement of loose seton with or without abscess drainage (88.6%) and drainage of low fistula with abscess trough fistulectomy or fistulotomy (11.4%). Four (5.1%) patients had infectious post-operative complications (abscesses). A second subsequent surgery was required in 53.2% of the patients, and 5.1% needed more than 12 surgeries. Seven-point two percent from the 79 patients were operated on an elective basis and 82.3% by an experienced colorectal surgeon. After "1st surgery the median follow-up duration was 85 months (Q1=37 and Q3=124) (*table 3*).

When there was minimal suppuration and little inflammation of the cPF under biologic treatment, the setons were removed, which allowed direct healing in 22 patients (27.8%) (*table 4*). A second or more local

Table 4 - Long-term clinical outcomes of the 79 patients with Crohn´s complex perianal fistula at the end of follow-up [a]

Clinical response	n pts [b] (%)
Response after "1st surgery"[c] (seton placement) + biologic	30 (38.0)
Complete:	22
Partial:	8
- setons removal	- 6
Response after ≥ 2 surgeries + biologic	32 (40.5)
Complete	23
Partial	9
- setons removal	- 4
Nonresponse or clinical recurrence	17 (21.5)

[a] Median follow-up of 85 months (interquartile range 37-124); [b]pts: patients; [c]"1st surgery": 1st surgery at the Santo António Local Health Unit (SALHU);

surgical procedures were performed in 32 patients (40.5%) with a complete response in 23 (29.1%) and partial in 9 (11.4%) (*table 4*).

After having previously undergone multiple surgeries, 2 patients had treatment with MSCs (*table 3*). They achieved a complete clinical response at 24 weeks, which was maintained at 52 weeks and 50 weeks of follow-up.

In which concerns to the 12 rectovaginal fistulas, all patients had seton placement, with 7 complete responses. According to the partial or total response of fistulous tract(s) and/or proctitis under biologic treatment, fibrosis has been observed with partial or complete obliteration of the ano/rectovaginal fistula after seton removal. However, one of them required an additional transperineal approach with anatomic reconstruction and advancement flap repair, with complete healing. Four patients had partial responses, in 3 of which setons could be removed resulting in gases emission only during defecation well tolerated by patients. Another patient who underwent a previous colostomy required a protectomy.

Averall, 3 patients (3.8%) required diversion stomas (*table 3*), which over time became permanent due to refractoriness to treatment. Three other patients required protectomy due to irreversible perineal destruction (one of them with abdominoperineal resection for suspected carcinoma).

Twenty-three of the 79 patients (29.1%) were previously under anti-TNFα treatment; and 53 did so at time of "1st surgery" (67.1%) (*table 5*). About half of the patients (55.7%) needed only one biologic until the last appointment of follow-up. However, due to perineal and/or luminal refractoriness to optimized treatment or due to low serum levels of biologic agents and/or high levels of respective antibodies, 17 patients (21.5%) required a second biologic, 10 a third (12,7%) and 6 a fourth one (7.6%) (*table 5*). Only 2 patients never received biologic treatment because they refused it, resulting in nonresponse (*table 6*).

More than 12 months after surgery, clinical remission was observed in 45 patients (57.0%) and partial response in 17 (21.5%), with a total of 78.5% reponse rate (*table 6*). From those patients with partial response setons removal were possible in 10 of them, as they had minimal symptoms (*table 4*). Seventeen patients (21.52%) did not respond to treatment (*table 6*).

To find out which variables were associated with

Table 5 - Biologic treatment of 79 patients with Crohn's complex perineal fistula in previous surgeries, in the "1st surgery" [a] and in subsequent surgeries

Biologic drugs	Previous surgery n pts [b] (%)	"1st surgery" n pts [b] (%)	Subsequent surgery n pts [b] (%)
No biologic [c]	56 (70.9)	21 (32.9)	2(2.5)
1 Anti-TNFα [d]	23 (29.1)	53 (67.1)	44 (55.7)
2 Anti-TNFα [d]	-	-	17 (21.5)
3 Biologic drug [e]	-	-	10 (12.7)
4 Biologic drug [e]	-	-	6 (7.6)

[a] "1st surgery": 1st surgery at SALHU; [b] pts: patients; [c] No biologic: defined by biologic suspension up to 6 months before surgery and beginning its administration 3 months after surgery [d] Anti-TNFα: Anti-Tumor necrosis factor α (Infliximab or Adalimumab); [e] 3º and 4ª Biologic drug: Vedolizumab or Ustekinumab

Table 6 – Clinical response of the Crohn's complex perianal fistula at the end of patient follow-up [a]

Response to treatment	No Biologic N pts [b] (%)	Biologic N pts [b] (%)	Total N pts [b] (%)
At last appointment	2	77	79 (100.0)
Complete	-	45	45 (57.0)
Partial	-	17	17 (21.5)
Nonresponse or clinical recurrence	2	15	17 (21.5)

[a] Median follow-up of 85 months (interquartile range 37-124); [b] pts: patients

worse outcome (n=17), simple logistic regression was performed with variables significant at 20% (*table 7*). Female sex and existence of high interesfincteric fistula, were protective factors for nonresponse to treatment (OR 0.34 (0.11; 1.09) p=0.070 and OR 0.30 (0.08; 1.14) p=0.077, respectively). Extraintestinal mucocutaneos manifestations (OR 2.75 (0.71; 10.61) p=0.141), number of surgeries >3 (OR 2.60 (0.87; 7.78) p=0.088), and supraesfincteric fistula (OR 4.62 (1.44; 14.87) p=0.10) were factors associated to risk of nonresponse or recurrence (*table 7*).

As shown in *table 8*, in the final model of the multivariate logistic regression analysis only the female sex and suprasphincteric fistula were associated with nonreponse: the first as a protective factor (OR 0.26 (0.07; 0.93) p=0.039) and the second as a risk factor (OR 5.88 (1.65; 20.94) p=0.006). This final model showed good adequability in the Hosmer & Lemeshow test (p-value=0.966).

DISCUSSION

In this retrospective study of a cohort of 79 patients with Crohn's cPF, experience with multimodal approach was evaluated as well as the relationship between different clinical variables and the response to biologic and surgical treatment. As already mentioned, all patients were discussed at a Multidisciplinary IBD Group consultation.

At the end of follow-up, 62 patients (78.5%) had a complete or partial clinical response. Seventeen (21.5%) had nonresponse or recurrence. In fact, these results are comparable to those reported in the literature (5,17,18). In the last decade 5-year disease recurrence rates of 40.1% (2013), 38.8% (2015) and 25% (2019) have been reported (19-21). According with Bouguen et al (2013), in a retrospective study of 156 patients with seton placement and IFX terapy, 108 (69.2%) had fistula closure. The cumulative probability of fistula recurrence was 16.6% and 40.1% at 1 and 5 years, respectively (19). In 2015, Lee et al also in a retrospective study of 227 patients reported a reoperation-free cumulative rates of 68.8%, 61.2%, and 50.5%, at 3-year, 5-year, and 10-year respectively (20). In 2019, Malian et al performed another retrospective study of 137 patients with Crohn' PD, including 120 treatead with anti-TNFα after drainage of fistulas and abscesses. Fistula-free survival was 74.5% at 5 years. In multivariated analysis biologic treatment and surgery approach was related with better long-term result; suspension of the anti-TNFα after fistula closure and colonic localization were linked to a shorter period free

Table 7 - Simple logistic regression. Outcome variable: group (62 patients with clinical response vs 17* patients with nonresponse or clinical recurrence at the end of follow-up)

	OR[a] (95% CI [b])	p-value
Age at diagnosis	1.01 (0.97; 1.06)	0.598
Sex		
Male	Reference	
Female	0.34 (0.11; 1.09)	0.070
Smoking Status		
Non-smoker	Reference	
Ex-Smoker	0.36 (0.04; 3.25)	0.365
Current Smoker	1.68 (0.54; 5.23)	0.367
Familial IBD [c]		
No	Reference	
Yes	0.79 (0.15; 4.03)	0.772
PF [d] as dominant complain of disease		
No	Reference	
Yes	1.52 (0.47; 4.84)	0.483
Montreal Classification – A [e]		
A1	Reference	
A2	0.46 (0.07; 2.83)	0.401
A3	0.80 (0.10; 6.25)	0.832
Montreal Classification 1st surgery – L [f]		
L1	Reference	
L2	1.70 (0.29; 10.09)	0.559
L3	1.59 (0.36; 7.01)	0.543
L1+L4	4.53 (0.75; 27.39)	0.100
L2+L4	NA[h]	NA[h]
L3+L4	NA[h]	NA[h]
Montreal Classification 1st surgery – B [g]		
B1	Reference	
B2	0.56 (0.14; 2.28)	0.420
B3	0.96 (0.22; 4.10)	0.950
Extraintestinal manifestations		
No	Reference	
Yes	2.75 (0.71; 10.61)	0.141
Mucocutaneous		
No	Reference	
Yes	0.29 (0.03; 2.42)	0.253
Musculoskeletal		
No	Reference	
Yes	0.89 (0.22; 3.61)	0.874
PF [d] type at "1st surgery"		
High Intersphincter		
No	Reference	
Yes	0.30 (0.08; 1.14)	0.077
Transsphincteric		
No	Reference	
Yes	0.73 (0.25; 2.15)	0.570
Extrasphincteric		
No	Reference	
Yes	3.81 (0.23; 64.34)	0.353
Suprasphincteric		
No	Reference	
Yes	4.62 (1.44; 14.87)	0.010
Rectovaginal		
No	Reference	
Yes	0.29 (0.03; 2.42)	0.253
Proctitis at "1st surgery"		
No	Reference	0.854
Yes	1.11 (0.37; 3.31)	0.838
CD duration until "1st surgery" (yrs)		
≤ 1	Reference	
>1 and ≤ 10	0.84 (0.24; 2.97)	0.791
>10	0.90 (0.23; 3.49)	0.879
Total Number of PF[d] Surgeries		
≤ 3	Reference	
> 3	2.60 (0.87; 7.78)	0.088
Biologic Drug		
One Anti-TNFα[i]	Reference	
>1 Anti-TNFα[i]	0.97 (0.33; 2.88)	0.955

[a]OR: Odds ratio; [b]CI: Confidence intervals; [c]IBD: inflammatory bowel disease; [d]PF: perianal fistulas; [e]A: Age(yrs), A1: <17; A2: 17–40; A3: >40; [f]L: Location, L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper disease, [g]B: Behavior, B1: nonstricturing, nonpenetrating, B2: structuring, B3: penetrating, p: perianal disease (2); [h]NA: not applicable; [i]Anti-TNFα: Anti-Tumor necrosis factor α; Bold: significant at 20%. *Outcome variable: patients without response – 17

Table 8 - Multiple logistic regression (outcome variable: patients with nonresponse or clinical recurrence at the end of follow-up).

	Initial Model		Final Model	
	OR[a] (95% CI[b])	p-value	OR[a] (95% CI[b])	p-value
Sex				
Male	Reference		Reference	
Female	0.26 (0.07; 0.96)	0.043	0.26 (0.07; 0.93)	0.039
Extraintestinal manifestations				
No	Reference			
Yes	2.11 (0.48; 9.22)	0.323		
PF[c] type at 1st surgery				
High Intersphincteric				
No	Reference			
Yes	0.38 (0.09; 1.63)	0.193		
Suprasphincteric				
No	Reference		Reference	
Yes	4.68 (1.27; 17.21)	0.020	5.88 (1.65; 20.94)	0.006
Total Number of PF[c] Surgery				
≤ 3	Reference			
> 3	1.45 (0.41; 5.15)	0.567		

[a]OR: Odds ratio; [b]CI: Confidence intervals; [c]PF: Perianal fistulas Bold: significant at 5%

of relapse (21). In 2020 editorial paper, Lukin suggests that the combination of surgical and medical approach is fundamental for favourable clinical results, and that the maintenance of an Anti-TNFα treatment contributes for a longer clinical remission (22).

In this serie of 79 patients, conservative surgery combined with generally long-term biologic treatment resulted in tolerable to good results. The main approach to ano /rectovaginal fistulas was seton placement and biologic therapy which resulted in complete response in 7 patients. Four patients had a partial response with minimal residual complains. One patient had nonresponse requiring protectomy. Recently, Otero-Piñeiro et al (23) in a retrospective review of 166 adult patients with a Crohn's-related rectovaginal fistula, concluded that over two-thirds can achieve complete response. Multiple surgical interventions, smoking and seton placement should be avoided because they negatively affect healing rates. But, in fact, there is little evidence in the literature about the most effective treatment of rectovaginal fistulas (8).

In statistic analysis, female sex was an independent protective factor for nonresponse of cPF (*table 8*). In most trials, sex was not associated with outcome (24-26). However, in a randomized controlled trial of IFX versus placebo (n = 94), Present et al found that males were significantly more likely to reach ≥50 percent reduction of draining fistulas at two or more consecutive study visits (p<0.001) (16). Haennig et al. (n = 81), in an observational study found that time interval until closure of fistulas was significantly shorter in men than in women, 11.7 months versus 21.0 months (p = 0.03) [HR 0.59, (95% CI 0.36-0.96)] (27).

Regarding fistula morphology, it was found that supraestincteric fístulas have a significativly worse clinical response than the others (*table 8*). As already mentioned, unfortunately few patients had imaging evaluation. In true, several studies showed that MRI classification is predictive of patient outcome (28,29). Torkzad et al, report that the MRI classification used at St James's University Hospital (29) is correlated with treatment outcomes. They showed that supralevator, transelevator and transsphincteric fistulas, and the latter associated with abscesses or secondary tracts in the ischioanal or ischiorectal fossa, were related with a less favorable outcome - leading to recurrence requiring further surgery (30). In a meta-analysis on prognostic factors for PF treatment, Z. Mei et al, concluded that suprasphincteric tracts have one of the highest recurrence rates - wich increases further if an internal orifice is not detected (31). Colorectal surgeons should obtain a clear anatomy of the cPF through preoperative clinical assessment, preferably complemented with imaging such as pMRI.

There are limitations to be considered in this retrospective study. It was not possible to classify anatomy and activity of cPF through imaging exams complementary to clinical examination. Even if explained by the reference to a tertiary centre, the high number of ano/rectovaginal fistula can result in a bias. Furthemore, the results of simple and multiple logistic regression analysis may have been influenced by the retrospective study, the small number of patients, different form of treatment and of duration of follow-up, resulted in heterogeneity of the variables. This may have been one of the reasons for

identifying only two prognostic factors related to long-term outcome. However, this study represents the real-world practice of a tertiary reference centre.

CONCLUSION

Complete or partial response was obtained in 78.5% of patients with Crohn's complex perianal fistulas who underwent combined biologic and surgical treatment. Suprasphincteric fistula was a risk factor for worse disease outcome and female sex was a protective factor for nonresponse. Treatment outcomes can be improved with multimodal therapy, the identification of predictors of long-term clinical response, and the emergence of new therapeutic weapons.

Author's contributions

Ana Cristina Silva - study design, data interpretation, drafting and review of the manuscript; Ezequiel Silva - data collection; Pedro Brandão - data collection; Mónica Sampaio - data collection; Andreia Teixeira - statistical analysis; Paula Lago - study design, data interpretation, drafting and review of the manuscript; Marisa Domingues Santos - supervision, study design, data interpretation, drafting and review of the manuscript. All authors contributed and approved the final version.

Disclosure statement

The authors declare that they have no conflict of interest.

Statement of funding

The authors declare that there is funding by CHUPorto 2022 Scholarship, financed by the Research and Development Fund of the Santo António Local Health Unit.

Ethical considerations

Study protocol was approved by the Ethics Committee of the SALHU [Ref.ª: 2021.152 (124-DEFI/127-CE)].

All procedures performed were in accordance with ethical standards and the 2013 Declaration of Helsinki (7th revision).

All information was treated in accordance with the provisions of Law Nº.58/2019, which ensures the implementation of Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of data.

REFERENCES

1. Kaplan GG, Bernstein CN, Coward S, Bitton A, Murthy SK, Nguyen GC, et al. The impact of inflammatory bowel disease in Canada 2018: epidemiology. J Can Assoc Gastroenterol. 2019; 2(Suppl 1):S6-S16.
2. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53.
3. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769-2778.
4. Bolshinsky V, Church J. Management of Complex Anorectal and Perianal Crohn's Disease. Clin Colon Rectal Surg. 2019;32(4): 255-260.
5. Yassin NA, Askari A, Warusavitarne J, Faiz OD, Athanasiou T, Phillips RKS, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment Pharmacol Ther. 2014;40(7):741-9.
6. Wang X, Shen B. Advances in Perianal Disease Associated with Crohn's Disease-Evolving Approaches. Gastrointest Endosc Clin N Am. 2019;29(3):515-530.
7. Vasudevan A, Bruining DH, Loftus EV Jr, Faubion W, Ehman EC, Raffals L. Approach to medical therapy in perianal Crohn's disease. World J Gastroenterol. 2021;27(25):3693-3704.
8. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. J Crohns Colitis. 2020;14(2):155-168.
9. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020;14(1):4-22.
10. Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160(7):2496-2508.
11. Wilhelm A, Fiebig A, Krawczak M. Five years of experience with the FiLaC™ laser for fistula-in-ano management: long-term follow-up from a single institution. Tech Coloproctol. 2017;21(4):269-276.
12. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. Gastroenterology. 2018;154(5):1334-1342.e4.
13. Pogacnik JS, Salgado G. Perianal Crohn's Disease. Clin Colon Rectal Surg. 2019;32(5):377-385.
14. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB. American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003;125(5):1508-30.
15. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. Br J Surg. 1976;63(1):1-12.
16. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398-405.
17. Lopez N, Ramamoorthy S, Sandborn WJ. Recent advances in the management of perianal fistulizing Crohn's disease: lessons for the clinic. Expert Rev Gastroenterol Hepatol. 2019;13(6):563-577.
18. Kotze PG, Shen B, Lightner A, Yamamoto T, Spinelli A, Ghosh S, et al. Modern management of perianal fistulas in Crohn's disease: future directions. Gut. 2018;67(6):1181-1194.
19. Bouguen G, Siproudhis L, Gizard E, Wallenhorst T, Billioud V, Bretagne JF, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol. 2013;11(8):975-81.e1-4.
20. Lee JB, Yoon SG, Park KJ, Lee KY, Kim DD, Yoon SN, et al. Korean IBD Study Group. The Clinical Features and Predictive Risk Factors

for Reoperation in Patients With Perianal Crohn Diseases; A Multi-Center Study of a Korean Inflammatory Bowel Disease Study Group. Ann Coloproctol. 2015; 31(5):176-81.
21. Malian A, Rivière P, Bouchard D, Pigot F, Eléouet-Kaplan M, Favreau-Weltzer C, et al. Pedictors of Perianal Fistula Relapse in Crohn's Disease. Inflamm Bowel Dis. 2020;26(6):926-931.
22. Lukin DJ. Predictors of Perianal Fistula Relapse in Crohn's Disease. Inflamm Bowel Dis. 2020;26(6):932-933.
23. Otero-Piñeiro AM, Jia X, Pedersen KE, Hull T, Lipman J, Holubar S, et al. Surgical Intervention is Effective for the Treatment of Crohn's-related Rectovaginal Fistulas: Experience From a Tertiary Inflammatory Bowel Disease Practice. J Crohns Colitis. 2023; 17(3):396-403.
24. Ye BD, Yang SK, Cho YK, Hyoung Park S, Yang DH, Yoon SM, et al. Clinical features and longterm prognosis of Crohn's disease in Korea. Scand J Gastroenterol. 2010; 45(10):1178-85.
25. Luna-Chadid M, Pérez Calle JL, Mendoza JL, Vera MI, Bermejo AF, Sánchez F, et al. Predictors of response to infliximab in patients with fistulizing Crohn's disease. Rev Esp Enferm Dig. 2004;96(6):379-81; 382-4. English, Spanish
26. Dewint P, Hansen BE, Verhey E, Oldenburg B, Hommes DW, Pierik M, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistulae closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). Gut. 2014;63(2):292-9.
27. Haennig A, Staumont G, Lepage B, Faure P, Alric L, Buscail L, et al. The results of seton drainage combined with anti-TNFalpha therapy for anal fistulae in Crohn's disease. Colorectal Dis. 2015;17(4): 311-9.
28. van Rijn KL, Meima-van Praag EM, Bossuyt PM, D'Haens GR, Gecse KB, Horsthuis K, et al. Fibrosis and MAGNIFI-CD Activity Index at Magnetic Resonance Imaging to Predict Treatment Outcome in Perianal Fistulizing Crohn's Disease Patients. J Crohns Colitis. 2022;16(5):708-716.
29. Morris J, Spencer JA, Ambrose NS. MR imaging classification of perianal fistulas and its implications for patient management. Radiographics. 2000;20(3):623-35; discussion 635-7.
30. Torkzad MR, Karlbom U. MRI for assessment of anal fistulae. Insights Imaging. 2010;1(2):62-71.
31. Mei Z, Wang Q, Zhang Y, Liu P, Ge M, Du P, et al. Risk Factors for Recurrence after anal fistula surgery: A meta-analysis. Int J Surg. 2019<69:153-164.