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Alimentary Tract

The timing of early therapeutic strategies has a significant impact on Crohn's disease prognosis

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ABSTRACT

Background: Abdominal surgery and immunosuppressive pharmacological treatments are two different therapeutic options used to manage Crohn disease. This study aimed to determine whether the timing of these interventions had an impact on patients' prognosis.
Method: This manuscript entails a retrospective analysis of a multicentric cohort involving 498 CD patients that had bowel surgery after diagnosis and prior to immunosuppression treatments. Two endpoints were considered: the occurrence of disabling disease and the need to undergo further bowel surgeries.
Results: Disabling disease affected 71% of all patients, whereas 39% needed reoperation. The odds ratios (OR) of being affected by disabling disease were higher when patients had upper tract involvement [3.412 [1.285–9.061]], perianal disease (2.270 [1.239–4.157]) and a longer time elapsed from diagnosis to first surgery (13–36 months: 2.576 [1.207–5.500]). On the other hand, the need to undergo further surgical interventions was significantly increased in smoking patients (2.294 [1.187–4.432]), but decreased in patients who started pharmacological therapy not later than six months after the first surgery (0.256 [0.093–0.704]).
Conclusions: Our results suggest that the timing of therapeutic strategies does affects the CD outcomes: whereas an early surgery had a preventive effect on the occurrence of disabling events, the introduction of medication in the first semester after surgery had a preventive effect on the need for reoperation.

1. Introduction

Crohn's disease (CD) is an immune-mediated inflammatory disease that can virtually affect the entire gastrointestinal tract, although its most common location is the colon and/or ileum. As a chronic disease, CD is characterized by frequent relapses and a deep impact in health-related quality of life [1]. So far, there is no definitive treatment for CD: current therapies aim to alleviate the symptoms and to improve patients' quality of life [2]. Bowel surgery is one of those therapies: approximately 50% of CD patients require bowel surgery within 10 years of diagnosis [3,4], whereas a total of 80% will eventually require surgery during their lifetime [5,6]. Surgery has an obvious important impact in patients' quality of life, and is also known to play a role in the disease outcomes afterwards, namely the occurrence of disabling events and recurrence

Recurrence in CD is extremely frequent and, according to the literature, affects 40%–80% of all patients [7,8]. The occurrence of disabling events (known as disabling disease) is not as easy to

Data described in this paper has not been previously presented anywhere.
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estimate, as the notion of "disabling" is rather dynamic and has been changing over the years. This concept was initially introduced by Beaugerie et al. in 2006 [9] and Loly et al. in 2008 [10], who performed an evaluation of the disease's impact according to measurable clinical criteria. Those studies reported a proportion of disabling disease of 85% and 58%, respectively. Later on, Yang et al. [11] used a slightly different definition of disabling disease – reflecting the new strategies for disease control meanwhile established – and reported a proportion of 80%.

As previously mentioned, surgery in CD patients impacts not only their quality of life, but also their likelihood of experiencing certain outcomes afterwards. As so, the characterization of the different variables associated to surgery and the definition of their specific impact in the natural evolution of the disease are key steps in preventive strategies. In this context, this work's main goal was to identify the effect of the timing of the first bowel surgery (after diagnosis) and immunosuppressive medication onset on two important CD outcomes: the occurrence of disabling events and the need for further surgeries.

2. Methods

2.1. Patients and collected variables

All patients gave consent for the collection of data in the Portuguese Inflammatory Bowel Disease database. Also, this database has been authorized by the Comissão Portuguesa de Protecção de Dados (authorization nr 2868/2013).

This study consisted in a retrospective analysis of a multicentric cohort of 498 patients who underwent bowel surgery after CD diagnosis and prior to any pharmacological treatment (immunosuppression [azathioprine and metotrexato] and/or biologic therapy). Patients were enrolled in the study according to the following inclusion criteria: 1) a definitive diagnosis of CD; 2) at least three years of follow-up; 3) at least one appointment with one of the physicians involved in this study during 2014 and 2015; and 4) at least one X-ray computed tomography (CT) or one magnetic resonance imaging (MRI) during the follow-up.

Patients' selection and the respective variables' collection were performed using the Portuguese Inflammatory Bowel Disease study group (GEDII—Grupo de Estudo de Doenças Inflamatórias Intestinais) database (gediibasedados.med.up.pt) [12]. Disease location and behaviour were classified according to the Montreal criteria [13].

2.2. Outcomes assessment

This study's primary endpoints were: 1) the occurrence of disabling disease; and 2) reoperation. Disabling disease was a composite endpoint defined by the presence of at least one of the following events [4,15]: one or more abdominal surgeries or two hospital admissions during the follow-up period; steroid dependence or steroid refractoriness; need for switching the first immunosuppressive drug or anti-TNFα agent; and the appearance of new clinical events after the index episode (stenosis, anal disease or penetrating disease). Steroid dependence was defined as the inability to reduce steroids below the equivalent of 10 mg per day, prednisolone within three months of starting steroids without recurrent active disease, or disease relapse within three months of stopping steroids; steroid resistance was defined as the presence of active disease despite a prednisolone dose of up to 0.75 mg kg^{-1} per day over a period of four weeks [16]. Reoperation was defined as the need for further surgeries after the initial one.

Table 1
Demographical and clinical variables (n = 498) of the cohort analysed in this study.

	n	%
Gender		
Male	227	46%
Female	271	54%
Smoking habits		
Never smoke	236	53%
Ex-smoker	99	22%
Smoker	108	25%
Age at diagnosis		
A1—≥16 years	50	10%
A2—17–40 years	364	73%
A3—>40 years	84	17%
Location		
L1—Ileo	247	54%
L2—Colonic	31	7%
L3—IleoColonic	177	39%
L4 (upper tract involvement)		
No	426	90%
Yes	48	10%
Behaviour		
B1—non-stricturing/non-penetrating	69	15%
B2—stricturing	185	39%
B3—penetrating	220	46%
Perianal disease		
No	385	77%
Yes	113	23%
Immunosuppression[a]		
None	158	32%
0–6 months	65	13%
7–12 months	18	4%
13–36 months	219	44%
>36 months		
Biologic therapy		
None	280	56%
0–6 months	13	3%
7–12 months	8	2%
13–36 months	24	5%
>36 months	173	35%
Immunosuppression and/or biologic therapy		
None	113	23%
0–6 months	72	15%
7–12 months	21	4%
13–36 months	42	8%
>36 months	250	50%
Time elapsed between diagnosis and surgery		
0–6 months	196	43%
7–12 months	43	9%
13–36 months	67	15%
>36 months	151	33%
Disabling disease	356	71%
Reoperation	192	39%

[a] Immunosuppression considered: azathioprine and metotrexato.

2.3. Statistical analyses

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, interquartile (IQR) range, and minimum and maximum, when appropriate. Hypothesis regarding categorical variables were tested using a Chi-square test or a Fisher's exact test, as appropriate. The time elapsed from surgery to disabling disease or reoperation was evaluated using survival analysis.: the cumulative probabilities of event-free survival were estimated using the Kaplan–Meier method and the LogRank and Breslow tests.

Logistic regression was applied to determine the relationship between clinical and demographical factors and the occurrence of disabling disease and reoperation. Moreover, Cox regression was applied to further characterize time to event (disabling disease or reoperation). Models were built according to the backward stepwise approach. All reported p-values were two-sided, and the significance level was set at 5%. All data were arranged, processed

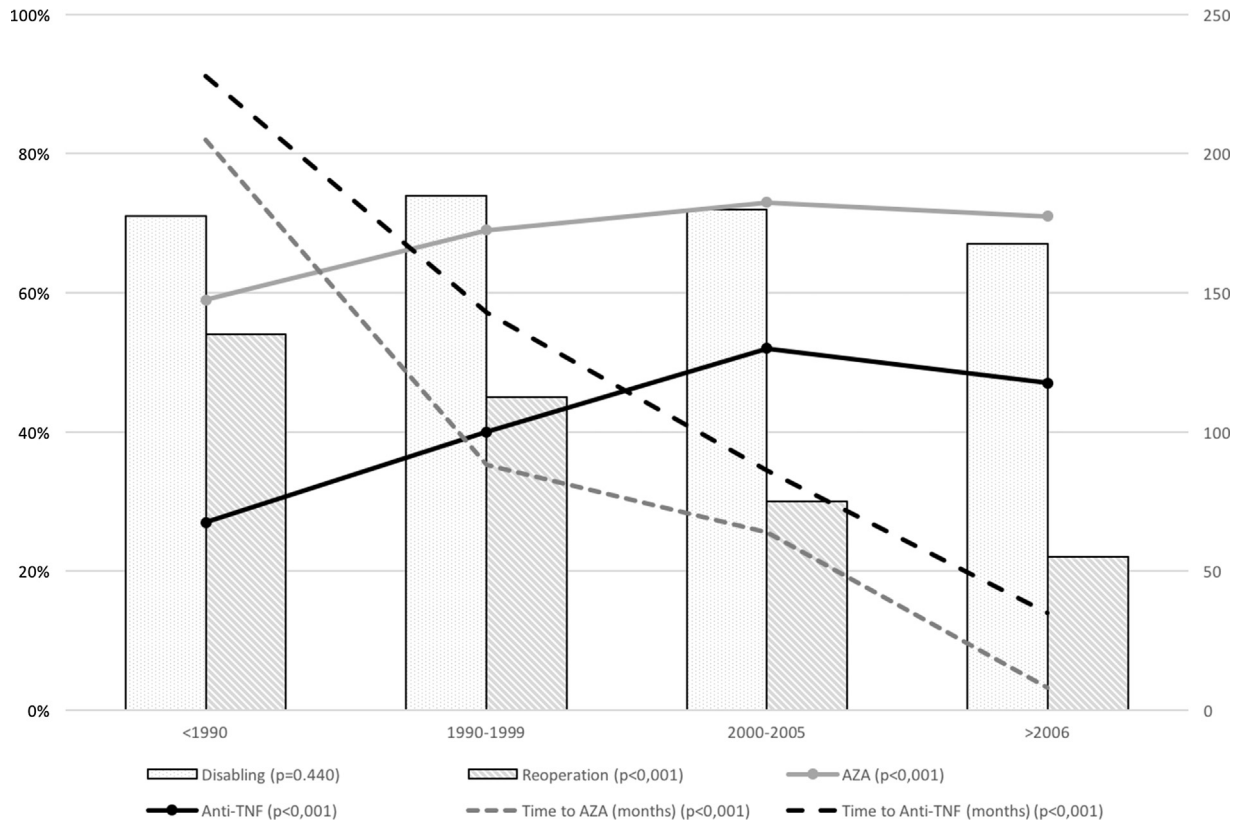

Fig. 1. Outcomes and immunosuppression onset stratified by year of diagnosis. The white bar represents the proportion (%) of patients with disabling disease ($p = 0.004$) and the grey bar patients with reoperation ($p < 0.001$). The full lines represent the proportion (%) of patients who were under immunosuppression (grey line $p < 0.001$) or biologic therapy (black line $p < 0.001$). The time of introduction of pharmacologic therapy in days was represented by grey dot line for immunossuppressors ($p < 0.001$) and black dot line for biologic therapy ($p < 0.001$).

and analysed with SPSS® v.23.0 (Statistical Package for Social Sciences).

3. Results

3.1. Cohort characterization

The patients included in this cohort (498) had, as a distinctive trace, the fact that they were all subjected to a bowel surgical intervention after CD diagnosis and prior to any pharmacological therapy (*i.e.*, before being placed on immunosuppressive drugs and biologic agents). Collected data includes baseline characteristics and follow-up information for a median of 16 (IQR—11–25) years (Table 1). Most patients were female (54%), and 53% of them have never smoked. In most cases (73%) the diagnosis was made during young adulthood (17–40 years). Isolated colonic location was present in 7% of the patients, whereas 10% were reported to have upper tract involvement. Concerning behaviour, the majority of patients had a severe form of the disease: 39% had stricturing and 46% had penetrating disease; moreover, 23% of all patients had perianal disease. Seventy-seven percent of the patients were placed on immunosuppressive drugs and/or anti-tumour necrosis factor α (anti-TNFα) during the follow-up time. For most of them (44%), the onset of pharmacological therapy was more than 36 months after the initial bowel surgery. The time elapsed between diagnosis and surgery was unevenly distributed: whereas most patients (43%) had their surgery within six months of diagnosis, for 33% the surgery occurred more than 36 months after diagnosis. For 9% and 15% of the patients the time elapsed was 7–12 and 13–36 months, respectively. Overall, 356 (71%) of patients experienced disabling disease, and 192 (39%) required one (or more) additional bowel surgery(ies).

To analyse the evolution of pharmacological therapy onset and outcomes along time, patients were stratified according to their year of diagnosis (<1990, 1990–1999, 2000–2005 and >2005)—Fig. 1. Whereas the occurrence of disabling disease remained stable along time ($p = 0.740$), the proportion of patients requiring additional bowel surgeries had decreased ($p < 0.001$). Moreover, the time elapsed from first surgery to the onset of immunosuppressive therapies had decreased in a significant fashion (Fig. 1).

The timing of the first bowel surgery did not seem to affect the proportion of patients starting pharmacological therapy at different time points ($p = 0.175$, data not shown). When evaluating AZA and anti-TNF separately, there were no significant differences for AZA ($p = 0.139$), but for anti-TNF the introduction occurred later in patients that had an early surgery (less than 6 months after diagnosis) than for patients that had a late one (more than 36 months after diagnosis)—120 *vs.* 80 months, $p = 0.050$.

3.2. Disabling disease

During the follow-up period analysed in this study, 356 (71%) patients were classified as having disabling disease (Table 1). The association between demographic and clinical variables and the occurrence of events that defined the disabling condition is depicted on Table 2: age at diagnosis, upper tract involvement, perianal disease and time elapsed from diagnosis to surgery were significant. Overall, diagnosis at 17–40 years old, upper tract involvement and perianal disease were statistically associated with

Table 2
Association between disabling disease and demographic/clinical aspects.

	Disabling									
	No (n = 142,29%)			Yes (n = 356,71%)				Adjusted association measures[b]		
	n	Col%	Row%	n	Col%	Row%	p-Value[a]	OR	95%IC	p-Value
Gender							0.346			
Male	60	42%	26%	167	47%	74%		–	–	–
Female	82	58%	30%	189	53%	70%		–	–	–
Smoking habits							0.266			
Never smoke	74	57%	31%	162	52%	69%		–	–	–
Ex-smoker	31	24%	31%	68	22%	69%		–	–	–
Smoker	25	19%	23%	83	27%	77%		–	–	–
Age at diagnosis							**0.003**			
A1	16	11%	32%	34	10%	68%		–	–	–
A2	90	63%	25%	274	77%	75%		–	–	–
A3	36	25%	43%	48	13%	57%		–	–	–
Location							0.170			
L1	79	61%	32%	168	52%	68%		–	–	–
L2	7	5%	23%	24	7%	77%		–	–	–
L3	43	33%	24%	134	41%	76%		–	–	–
L4							**0.009**			
No	26	19%	38%	43	13%	62%		**Ref**		
Yes	47	35%	25%	138	41%	75%		**3.412**	**1.285–9.061**	**0.014**
Behaviour										
B1	26	19%	38%	43	13%	62%	0.157	–	–	–
B2	47	35%	25%	138	41%	75%		–	–	–
B3	63	46%	29%	157	46%	71%		–	–	–
Perianal disease							**0.002**			
No	123	87%	32%	262	74%	68%		**Ref**	–	–
Yes	19	13%	17%	94	26%	83%		**2.270**	**1.239–4.157**	**0.008**
Time between diagnosis and surgery							0.053			**0.072**
0–6 months	72	51%	34%	137	39%	66%		**Ref**		
7–12 months	13	9%	27%	35	10%	73%		1.818	0.766–4.318	0.175
13–36 months	13	9%	18%	59	17%	82%		**2.576**	**1.207–5.500**	**0.014**
>36 months	44	31%	27%	120	34%	73%		1.290	0.780–2.136	0.322
Hosmer–Lemeshow	–	–	–	–	–	–		**0.370**		
Roc	–	–	–	–	–	–		**0.641 [0.586–0.695]**		

Bold values are statistically significant values, i.e., the p-value is less than the significance predefined for the study (5%).
[a] Chi-square test; OR—odds ratio; 95% CI—95% confidence interval.
[b] Multivariate logistic regression model.

the occurrence of disabling disease. Moreover, a later first surgery was also associated with disabling disease.

A multivariable logistic regression was performed to determine which factors were independent predictors of disabling disease (Table 2). This analysis included all collected variables with the exception of the utilization of medical therapies, as this variable is involved in the disabling definition used in this study. The results show that the odds ratio (OR) of experiencing disabling disease during follow-up was increased for patients with upper tract involvement (OR = 3.412 CI95% [1.285–9.061]), perianal disease (OR = 2.270 [1.239–4.157]), and a longer time elapsed from diagnosis to the first bowel surgery (significant only for the interval 13–36 months: OR = 2.576, CI95% [1.207–5.500]). A multivariate Cox regression was also performed but none of the above mentioned factors were shown to be independent predictors of time to disabling disease (data not shown).

3.3. Reoperation

During the follow-up period analysed in this study, 192 (39%) of all patients needed to through at least one additional abdominal surgery (Table 1). The following factors were shown to be associated with the need for reoperation: age at diagnosis, disease behaviour, presence of perianal disease and the timing of introduction of pharmacological therapy (Table 3). Patients who were diagnosed as young adults, who were placed under immunosuppression late after surgery, and that had structuring behaviour or perianal disease were statistically associated with the need for reoperation. Concerning time between surgery and reoperation, patients who were younger at diagnosis had a higher median time (≤16 years: median = 276, 95%CI: [151–400] and 17–40 years: median 192 [157–226]. Also, patients without immunosuppression and/or biologic therapy during the follow-up had a higher median time than other patients (none: 474 [292–655]; 13–36 months: 123 [85–160] and >36 months: 171 [150–192]). Median time to reoperation was lower in patients with penetrating disease (B3: 218 [142–293]) and in patients with perianal disease (186 [87–284])—Fig. 2.

The multivariable logistic regression showed that two variables were independent predictors of reoperation: smoking habits and timing of the pharmacological intervention (Table 3). The risk of requiring a reoperation during the follow-up period were increased for smoking patients (OR = 2.294, CI95% [1.187–4.432]), and decreased for patients whose immunosuppressive or biologic therapy onset was within six months of surgery (OR = 0.256, CI95% [0.093–0.704]). Moreover, a multivariable Cox regression showed that behaviour (B2: HR = 2.049, CI95% [1.044–4.021] and B3: HR = 2.042 CI95% [1.046–3.982]), perianal disease (HR = 1.669 CI95% [1.174–2.373]) and introduction of immunosuppression and/or biologic therapy (7–12 m: HR = 3.910 [1.482–10.361], 13–36 m:

Table 3
Reoperation in patients with abdominal surgery after diagnosis (n = 767).

	Reoperation									
	No (n = 306,61%)			Yes (n = 192,39%)			p-Value[a]	Adjusted association measures[b]		
	n	Col%	Row%	n	Col%	Row%		OR	95%IC	p-Value
Gender							0.167			
Male	132	43%	58%	95	49%	42%		–	–	–
Female	174	57%	64%	97	51%	36%		–	–	–
Smoking habits							0.091			**0.042**
Never smoke	157	57%	67%	79	47%	33%		**Ref**		
Ex-smoker	59	21%	60%	40	24%	40%		1.492	0.778–2.682	0.228
Smoker	59	21%	55%	49	29%	45%		**2.294**	**1.187–4.432**	**0.013**
Age at diagnosis							**0.002**			
A1	31	10%	62%	19	10%	38%		–	–	–
A2	209	68%	57%	155	81%	43%		–	–	–
A3	66	22%	79%	18	9%	21%		–	–	–
Location							0.294			
L1	155	56%	63%	92	52%	37%		–	–	–
L2	22	8%	71%	9	5%	29%		–	–	–
L3	102	37%	58%	75	43%	42%		–	–	–
L4							0.134			
No	269	91%	63%	157	87%	37%		–	–	–
Yes	25	9%	52%	23	13%	48%		–	–	–
Behaviour										
B1	56	19%	81%	13	7%	19%	**0.002**	–	–	–
B2	106	36%	57%	79	44%	43%		–	–	–
B3	132	45%	60%	88	49%	40%		–	–	–
Perianal disease							**0.003**			
No	250	82%	65%	135	70%	35%		–	–	–
Yes	56	18%	50%	57	30%	50%		–	–	–
Time between diagnosis and surgery							0.940			
0–6 months	129	43%	62%	80	42%	38%		–	–	–
7–13 months	28	9%	58%	20	11%	42%		–	–	–
13–36 months	46	15%	64%	26	14%	36%		–	–	–
>36 months	100	33%	61%	64	34%	39%		–	–	–
Immunosuppression and/or biologic therapy							**<0.001**			**<0.001**
None	90	29%	80%	23	12%	20%		Ref		
0–6 months	58	19%	81%	14	7%	19%		**0.256**	**0.093–0.704**	**0.008**
7–12 months	14	5%	67%	7	4%	33%		0.609	0.166–2.235	0.454
13–36 months	23	8%	55%	19	10%	45%		0.884	0.325–2.409	0.810
>36 months	121	40%	48%	129	67%	52%		2.059	0.913–4.646	0.082
Hosmer–Lemeshow								**0.961**		
AUC ROC								**0.649 [0.597–0.701]**		

Bold values are statistically significant values, i.e., the p-value is less than the significance predefined for the study (5%).
[a] Chi-Square test; OR—odds ratio; 95% CI—95% confidence interval.
[b] Multivariate logistic regression model.

Table 4
Factors associates with reoperation in patients with previous surgery.

	Multivariate analysis		
	HR	95%IC	P
Behaviour			
B1	**Ref**		
B2	**2.049**	**1.044–4.021**	**0.037**
B3	**2.042**	**1.046–3.982**	**0.036**
Perianal disease			
No	**Ref**	**–**	**–**
Yes	**1.669**	**1.174–2.373**	**0.004**
Immunosuppression and/or biologic therapy			
None	**Ref**		
0–6 months	1.583	0.710–3.527	0.261
7–12 months	**3.919**	**1.482–10.361**	**0.006**
13–36 months	**3.921**	**1.894–8.116**	**<0.001**
>36 months	**3.281**	**1.868–5.763**	**<0.001**

HR—hazard ratio; 95% IC—95% confidence interval.
Bold values are statistically significant values, i.e., the p-value is less than the significance predefined for the study (5%).

HR = 3.921 [1.894–8.116] and >36m: HR = 3.281 [1.868–5.763]) were independent factors of time to reoperation (Table 4).

4. Discussion

CD patients are likely to need at least one abdominal surgery during the course of the disease. This study addresses the impact of the timing of an initial surgery and of the onset of immunosuppressive medication on CD prognosis, namely on the occurrence of disabling events and on the need of further surgeries.

This report highlights the evolution of therapeutic strategies, particularly the tendency to use a top-down approach, which is clearly reflected in the decrease of the time elapsed from surgery to the onset of immunosuppressive medication with the increase in the year of diagnosis. On the other hand, it should be noticed that the introduction of immunosuppressive therapy (AZA or anti-TNF) was not influenced by the time elapsed from diagnosis to first surgery. With the exception of a later introduction of anti-TNF in patients that had an early surgery, the time point at which patients underwent their initial surgery had no impact on the moment the

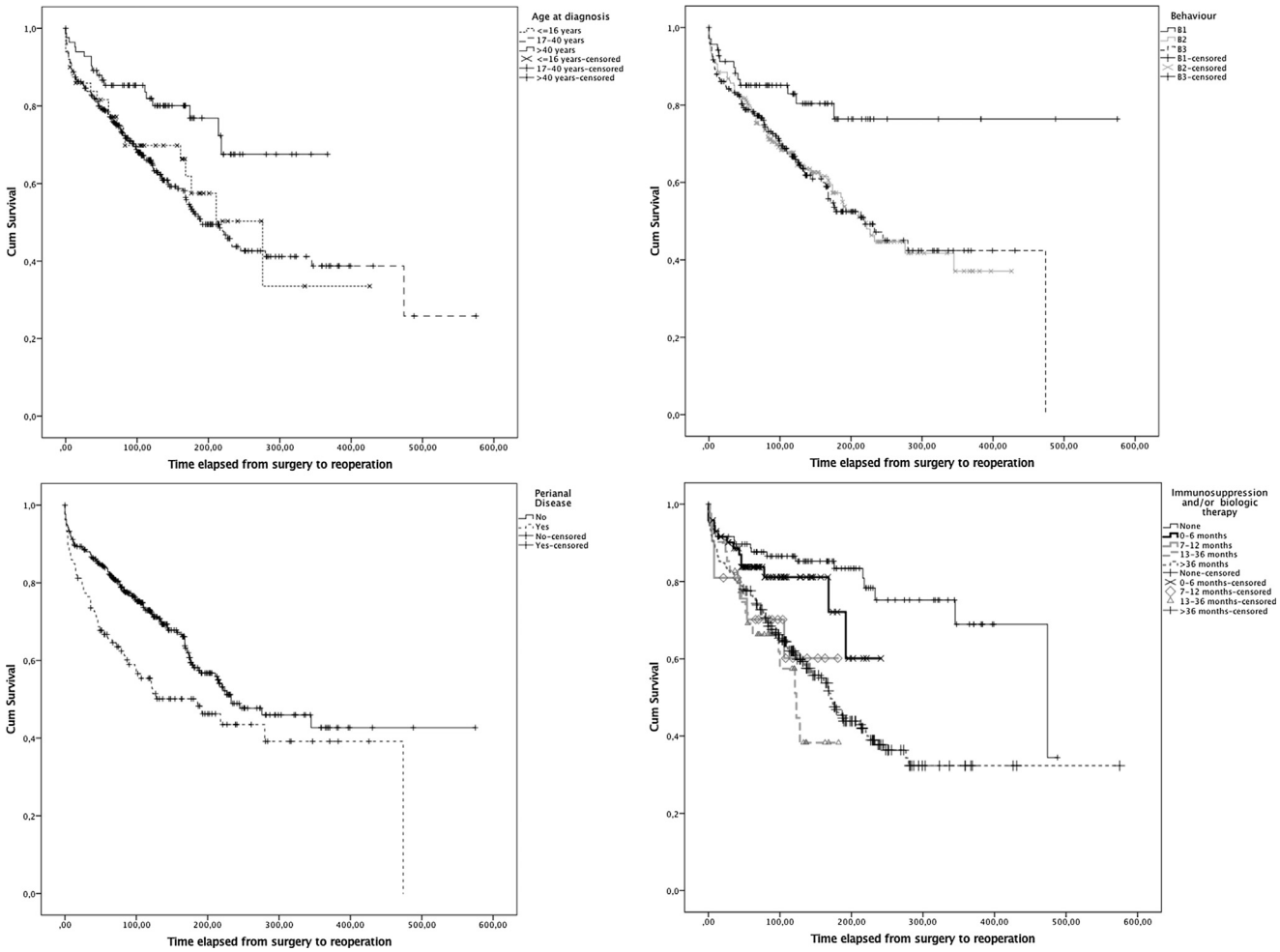

Fig. 2. Kaplan–Meier curves showing time to reoperation stratified by a) age at diagnosis: $p_{log\text{-}rank} = 0.007$, b) behavior: $p_{log\text{-}rank} = 0.009$, c) perianal disease: $p_{log\text{-}rank} = 0.004$, and d) immunosuppression and/or biologic therapy $p_{log\text{-}rank} < 0.001$.

medication was introduced. In other words, our results concerning the occurrence of disabling disease and need for reoperation were not biased by different therapeutic strategies regarding medication.

Disabling disease is an important outcome, and can be considered as a proxy of disease severity. The definition of disabling disease used in this study differed from that introduced in 2006 by Beaugerie et al. [9], and used by Loly et al. [10] and Yang et al. [11] in subsequent studies. The major difference concerns the introduction of immunosuppressive drugs, including anti-TNF, which was considered to be a disabling criterion in previous studies but not in this one. This evolution of the disabling concept is intimately linked with the increasing knowledge of the CD pathophysiology and development, which in turn is reflected into new top-down therapeutic strategies for disease control and symptoms management [17–19]. It should be highlighted that the disabling definition used in this study has been applied before and proved as useful [14,15,20]. Still, and despite using this updated and more restrictive definition of disabling disease, the disabling prevalence observed in this cohort (75%) is similar to that obtained in previous studies. Moreover, disease location, perianal disease and upper tract involvement were found to be independent predictors of disabling disease, which concurs with the published literature [21]. The main novelty in this study is the observation that the time elapsed from diagnosis to an initial surgery is also an independent predictor of disabling disease: in fact, patients that went through the first surgery shortly after diagnosis were less prone to suffer disabling disease during the follow-up period.

The term "reoperation" is used in this study as the need to undergo at least one additional abdominal surgery during the follow-up period, which constitutes a serious complication of CD. Multiple risk factors – patient-related, disease-related and surgery-related – have already been identified and are used to predict this outcome, although the literature fails to be consensual on this issue [22]. In this study, 39% of all patients needed reoperation, a similar result to what has been obtained previously [23,24]. A few studies have been published associating the introduction of medical therapeutics, namely immunosuppression, with reoperation. In fact, immunosuppression was considered to be relevant in the CD management particularly when introduced shortly after surgery as a prophylactic therapy [22]. Our study was not entirely conclusive in this regard, although the onset of medical therapeutics within six months of surgery was statistically associated to a lower risk of reoperation. Moreover, our results highlight that smoking is a risk factor for reoperation, an important implication that has already been shown in a previous study [25].

This study had a few important strengths that should be acknowledged: the cohort under analysis was large, multicentric, thoroughly characterized and data was retrieved for a long follow-up period (median of 16 years, IQR = 11–25). However, and as limitations, one should have into consideration that this was a retrospective study, endoscopic recurrence data were not available, and both outcomes were retrospectively-defined.

In conclusion, our study shows that the CD prognosis is influenced not only by the patients' and disease features (disease

location and behaviour, presence of perianal disease, involvement of the upper gastrointestinal tract and smoking habits), but also by the timing of the therapeutic strategies followed. In fact, an early surgery has a preventive effect on the occurrence of disabling disease, whereas the introduction of AZA or/and anti-TNF more than six months after the initial surgery seems to aggravate the risk for reoperation. The important clinical impact of these variables support their inclusion in the algorithms developed to back the decision-making aiding tools concerning the strategies followed for CD management.

Conflict of interest

Fernando Magro received a fee for presenting from: AbbVie, Ferring, Falk, Hospira, PharmaKern, MSD, Schering, Lab. Vitoria, Vifor, OmPharma.

All others authors: None declared.

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