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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

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