Prognostic models for Inflammatory Bowel Disease: evidence, classification and prediction

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Title

Prognostic models for Inflammatory Bowel Disease: evidence, classification and prediction

Modelos de prognóstico na Doença Inflamatória Intestinal: evidência, classificação e previsão

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Contents

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List of Publications

This thesis was based in several publications.

Research Papers and Abstracts

Prognostic factors for disabling Crohn's disease: a systematic review and meta-analysis.
World Journal of Gastroentereology 19(24): 3866-71, 2013.
Cláudia Camila Dias, Pedro Pereira Rodrigues, Altamiro da Costa Pereira, Fernando Magro

Clinical Predictors of colectomy in patients with ulcerative colitis: systematic review and meta-analysis of cohort studies.
Journal of Crohn's and Colitis, 9(2):156-163, 2015
Cláudia Camila Dias, Pedro Pereira Rodrigues, Altamiro da Costa Pereira, Fernando Magro

The impact of early surgery and immunosuppression on Crohn's disease disabling outcomes.
(*Inflammatory Bowel Diseases*, 23 (2):289-297, 2017)
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The timing of early therapeutics strategies has a significante impact on the Crohn's disease prognosis
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Preliminary study for a Bayesian network prognostic model for Crohn's disease.
Proceedings of 2015 IEEE 28th International Symposium on Computer-Based Medical Systems 141-144, 2015
Cláudia Camila Dias, Fernando Magro e Pedro Pereira Rodrigues

Disabling and reoperation in patients with Crohn's disease subject to early surgery or immunosuppression: A Bayesian network prognostic model. disease.
Proceedings of 2016 IEEE 29th International Symposium on Computer-Based Medical Systems 265-268, 2016
Cláudia Camila Dias, Fernando Magro e Pedro Pereira Rodrigues

EArly SurgerY or Immunosuppression - EASY study.
Journal of Crohn's and Colitis, 9(suppl 1):S317, 2015
Fernado Magro, Rosa Coelho, Samuel Fernandes, Ângela Rodrigues, Ana Oliveira, Paula Sousa, Rita Barosa, Pedro Boal Carvalho, Daniel Trabulo, Marta Eusébio, Joana Moleiro, Rita Herculano, Paula Peixe, Bruno Gonçalves, Henrique Morna, Helena Tavares, Luís Contente, Raquel Gonçalves, Paulo Caldeira, Isadora Rosa, Isabel Cremers, José Cotter, Ana Isabel Vieira, Paula Ministro, Francisco Portela, Cidalina Caetano, Paula Moura-Santos, Susana Lopes, Cáudia Camila-Dias

Oral Communications

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Development and validation of risk matrices for Crohn's disease outcomes in patients submitted to early therapeutic interventions

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Preliminary study for a Bayesian network prognostic model for Crohn's disease.

UEG 2015, Barcelona, Spain
October 15th-19th
Early surgery or immunossuppresion in Cronh's Disease Easy study

Abbreviations and Notation

CD: Crohn disease
UC: Ulcerative colitis
IBD: Inflammatory Bowel disease
NB: Naive Bayes
TAN: Tree Augmented Naive Bayes
AUC: Area Under the Curve
ROC: Receiver operating characteristics
OR: Odds Ratio
CI 95%: Confidence interval of 95%
Prev: Prevalence
IQR: Inter Quartile Range
Pretest: Pre-test probability
Acc: Accuracy
Sens: Sensitivity
Spec: Specificity
PPV: Positive predictive value
NPV: Negative predictive value
LR+: Positive likelihood ratio
LR-: Negative likelihood ratio
Odds post-test+: Positive post-test odds
Odds post-test-: Negative post-test odds

$+$: positive test
$\sim D$: no disease
D: disease
$p(D)$: probability of D occurs
$p(A, B)$: probability of A and B both occurs
$p(A|B)$: probability of A occurs given that B also occurs

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Abstract

Inflammatory bowel disease (IBD) is a chronic disease with unknown aetiology. The two most prevalent types of IBD are Crohn's disease and ulcerative colitis which, given their similarities, are often difficult to distinguish. Their chronic characteristics, along with a high risk of complications (including relapses, surgeries and disabling, among others) make it essential to develop accurate prediction models. The different published studies, developed to improve the prognosis, have been struggling as they show heterogeneous results, likely the result of using different methodologies and/or applying different criteria for patient selection and evaluation. In addition, predicting the prognosis is a task of considerable uncertainty, so the development of predictive models also requires research. These can be based on different factors, namely genetic, serologic, clinical and demographical, but the latter two are probability the easiest to use since they are faster to collect. Thus, it has become vital to identify and evaluate these clinical and demographic factors.

This work has three objectives: summarize the evidence regarding IBD outcomes and risk factors, identify and assess risk factors for identified outcomes, and develop and validate prognostic models for those outcomes, based on the identified factors.

In order to identify factors associated with the prognosis, systematic reviews and meta-analysis for Crohn's disease and ulcerative colitis were developed. Factors such as young age at diagnosis, perianal disease, initial use of steroids for the first flare and ileocolic disease location were identified as independent factors for disabling disease in Crohn's patients. Concerning ulcerative colitis, male gender, non-smoking habits, extensive disease, need for corticosteroids and hospitalization were associated with colectomy. In order to identify and assess risk factors for outcomes of Crohn's disease, an observational study, using an independent cohort of patients, was conducted. We have studied the impact of demographical and clinical factors (such as the timing of therapeutics strategies) on disabling disease and reoperation. Early surgery or immunosuppression seem to not prevent global disabling disease, but an early start of immunosuppression by itself is associated with fewer surgeries and should be considered in daily practice as a preventive strategy. Nonetheless, within surgical patients, an early surgery (within six months after diagnosis) can prevent disabling events, and the introduction of immunosuppressive medication more than one month after the initial surgery seems to increase the likelihood of needing further surgeries. The third objective of this thesis is to develop and validate prognostic models for the identified outcomes. Two main paths of work have been followed for modelling predictive classifiers, one based on Bayesian networks and the other on decision trees. Bayesian network models achieved high area under the curve (AUC) for disabling disease and reoperation, and were included in an online tool, allowing the application of the classifier at bedside. Risk matrices - based on age at diagnosis, perianal disease, disease aggressiveness and early therapeutic decisions - exhibited also good performance for the most important prognostic criteria: high positive post-test odds for disabling disease and low negative post-test odds for reoperation. The risk matrices seem also easily applicable as bedside clinical tools that can help physicians

during therapeutic decisions in early disease management. In the second path, decision trees were able to predict disabling, surgery and reoperation with high AUC, and were shown to be a valid and useful approach to depict outcome risks. The defined cut-off risk levels expressed high odds for a positive test for disabling, while excluding surgery and reoperation with low odds for a negative test.

In conclusion, clinical and demographical factors should be used more frequently in the prognosis of IBD as they are easier to collect than serologic or genetic ones. Factors such as age at diagnosis, behavior, perianal disease, and location are important predictors for negative outcomes and should, as soon as possible, be known. Concerning interventions, immunosuppression, as the first therapy after diagnosis, is effective in preventing future surgeries, being its efficiency higher upon an early start. On the other hand, patients undergoing an early surgery after diagnosis have an increased tendency to be re-operated, even with a concomitantly early start of immunosuppression therapy. Given this, predictive models for CD prognosis could enhance the initial approach and, therefore, improve the clinical outcome.

Resumo

A doença inflamatória intestinal (DII) é uma doença crónica e com etiologia desconhecida. As duas formas mais prevalentes de DII são a doença de Crohn e a colite ulcerosa que, dadas as suas semelhanças, são muitas vezes difíceis de distinguir. As suas características crónicas, acumuladas com um grande risco de complicações (nomeadamente recidivas, cirurgias e doença incapacitante, entre outras), tornam imprescindível o desenvolvimento de modelos de prognóstico. Os estudos desenvolvidos no intuito de melhorar esse prognóstico têm apresentado resultados muito díspares, fruto provavevelmente da utilização de diferentes metodologias e critérios de seleção e avaliação utilizados. Para além disso, a previsão do prognóstico reveste-se de elevada incerteza, pelo que o desenvolvimento de modelos preditivos requer também uma investigação mais aprofundada. Os modelos podem ser baseados em diferentes fatores, nomeadamente genéticos, serológicos, clínicos e demográficos, sendo estes últimos mais fáceis de usar, uma vez que são mais facilmente recolhidos tornando-se assim vital a sua identificação e utilização mais frequente.

Este trabalho tem três objetivos: o primeiro, resumir a evidência no que diz respeito aos factores de risco na DII, identificar e avaliar fatores de risco para diferentes *outcomes*, e desenvolver e validar modelos de prognósticos para os *outcomes* utilizados, com base nos fatores identificados.

Com o objectivo de identificar os fatores associados ao prognóstico, foram realizadas duas revisões sistemáticas e meta-análise para a doença de Crohn e colite ulcerosa. Fatores como idade ao diagnóstico menor que 40 anos, doença perianal, uso inicial de corticosteróides durante a primeira recaída e doença ileocólica foram identificados como fatores de risco independentes para a doença incapacitante nos pacientes com doença Crohn. No que diz respeito à colite ulcerosa, foram associados com a colectomia o sexo masculino, não-fumadores, doença extensa, necessidade de corticosteróides e de hospitalização . A fim de identificar e avaliar os fatores de risco na doença de Crohn, foi realizado um estudo observacional, utilizando uma coorte independente de pacientes, foi realizado. Foi também estudado o impacto de fatores demográficos e clínicos (como o tempo de introdução de terapêuticas farmacológicas) na doença incapacitante e na reoperação. A cirurgia precoce ou imunossupressão parece não prevenir a doença incapacitante, mas um início precoce da imunossupressão, por si só, está associado a menos cirurgias e deverá ser considerado na prática diária como uma estratégia preventiva. No entanto, em pacientes cirúrgicos, uma cirurgia precoce (nos primeiros seis meses após o diagnóstico) pode prevenir a doença incapacitante. Por outro lado a introdução de imunossupressores um mês após a cirurgia inicial parece aumentar o risco de reoperação. O terceiro objetivo desta tese é desenvolver e validar modelos de prognóstico para os *outcomes* identificados. Foram efetuadas duas abordagens na modelação: uma baseada em redes Bayesianas e a outra em árvores de decisão. Os modelos baseados nas redes Bayesianas apresentaram AUC elevadas tanto para a doença incapacitante como para a reoperação, tendo sido incluídos numa ferramenta online, que permite a aplicação diretamente na prática clínica. As matrizes de risco - com base na idade ao diagnóstico, a doença perianal, comportamento da doença e as

decisões terapêuticas precoces - exibiram também um bom desempenho para os critérios de prognóstico mais importantes: elevados odds pós-teste positivos para a doença incapacitante e baixos odds pós-teste negativos para a reoperação. As matrizes de risco podem ser facilmente aplicáveis como ferramentas clínicas podendo ajudar os clínicos durante as decisões terapêuticas com efeitos no percurso da doença. Na segunda abordagem, as árvores de decisão foram, também, capazes de prever doença incapacitante, a cirurgia e reoperação com valores altos de AUC, tendo sido mostrado que as árvores de decisão são uma abordagem válida e útil. Mais uma vez, para a doença incapacitante foram obtidos valores altos de odds pós-teste positivos e valores baixos de odds pós-teste negativos para a cirurgia e reoperação.

Em conclusão, fatores clínicos e demográficos devem ao ser usados com mais frequência no prognóstico da DII, uma vez que são mais fáceis e baratos de recolher do que os serológicos ou genéticos. Fatores como idade ao diagnóstico, comportamento da doença, doença perianal, e localização da doença são importantes preditores de maus *outcomes* e devem, logo que possível, ser conhecidos. No que diz respeito a intervenções precoces, a imunossupressão, como primeira abordagem da doença, é eficaz na prevenção de futuras cirurgias. Por outro lado, os pacientes submetidos a uma cirurgia precoce têm uma maior tendência para serem reoperados, mesmo com um início precoce da imunossupressão. Perante isto, modelos preditivos para o prognóstico na doença de Crohn poderiam reforçar a abordagem inicial à doença e, consequentemente, melhorar o seu resultado clínico.

1. Outline

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Although based on several different studies, this thesis conveys a consolidated message which is organized into several chapters.

Chapter 2 presents an introduction on inflammatory bowel disease (IBD) and clinical decision support. Also presented are the main statistical concepts of Bayesian networks, decision trees, and different validation methodologies.

Chapter 3 synthetizes the aim and specific objectives of this thesis.

Chapters 4, 5 and 6 present the main results of the different studies developed to achieved the three main objectives of the thesis.

Chapter 4 presents a synthesis of the main evidence, published in the literature, regarding outcomes and risk factors for Crohn's disease and ulcerative colitis.

Chapter 5 presents original cohort studies developed to identify and assess risk factors for Crohn's disease.

Chapter 6 presents the development and validation of predictive models for Crohn's disease prognosis, taking into account the outcomes defined in Chapter 4 and some of the risk factors found in Chapter 5.

Chapter 7 presents a brief discussion and some recommendations for the future of Crohns disease prognosis.

Appendix A and **B** include preliminary papers presented at two editions of an international symposium on computer-based medical systems, where the Bayesian network prognostic models were first studied and discussed.

Appendix C presents a screenshot and example of use of the online tool developed to allow the application of the Bayesian network classifier at bedside.

2. Rationale

2. Rationale

2.1 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic disease which involves all or part of the digestive tract. The most frequent diseases are Crohn's disease (CD) and ulcerative colitis (UC) [Devlin and Panaccione, 2010]. Ulcerative colitis might affect only the large intestine and can be classified according to its location and severity. The extent of the disease can be classified according to the Montreal classification [Dignass et al., 2012] into three categories presented in Table 2.1.

Table 2.1: Classification of Montreal - Extent of ulcerative colitis.

Extent	**Description**
E1: Ulcerative proctitis	involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2: Left side UC (distal UC)	involvement limited to a proportion of the colorectum distal to the splenic flexure
E3: Extensive UC (pancolitis)	involvement extends proximal to splenic flexure

Concerning severity, and using the Montreal classification [Satsangi et al., 2006], patients can be classified into five categories presented in Table 2.2.

Crohn's disease might affect both the large and the small intestine, being a transmural disease, afecting not only the mucosa but also the deeper layers [Latella et al., 2009, Devlin and Panaccione, 2010], being the ileum and colon the most commonly affected areas. The disease can also be classified according to location, behavior and age at diagnosis according to the Montreal classification [Dignass et al., 2010] as presented in Table 2.3.

The symptoms of the disease can be mild or severe depending of the severity of the disease. The main symptoms include diarrhoea, fever and fatigue, abdominal pain, blood in stool, reduction of appetite and consequently weight loss. These symptoms are common in the two inflammatory bowel diseases and, because of that, many times the differential diagnosis is very difficult to establish [Latella et al., 2009, Cosnes et al., 2002]. The diagnosis is made based on blood tests, endoscopic procedures (colonoscopy, sigmoidoscopy, upper endoscopy, capsule endoscopy or double-balloon endoscopy) and imaging procedures (x-ray, computerized tomography scan or magnetic resonance imaging).

Table 2.2: Classification of Montreal - Severity of ulcerative colitis.

Severity	**Description**
S0: Clinical remission	Asymptomatic
S1: Mild UC	Passage of 4 fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2: Moderate UC	Passage of more than 4 stools per day but with minimal signs of systemic toxicity
S3: Severe UC	Passage of least 6 blood stools/day Pulse rate of at least 90 beats/min Temperature of at least 37.5 Haemoglobin of least 10.5g/100ml ESR of at less than 30 mm/h

Table 2.3: Montreal classification for Crohn's disease

Age at diagnosis	
A1	<=16 years
A2	17-40 years
A3	>40 years
Location	
L1	Ileal
L2	Colonic
L3	Ileocolonic
L4	
Behavior	
B1	Non-Stricturing/penetrating
B2	Stricturing
B3	Penetrating
p	Perianal disease[2]

[1] L4 is a modifier that can be added to L1-L3
when concomitant upper gastrointestinal disease is present.
[2] "p" is added to B1-B3 when concomitant perianal disease is present.

The cause of IBD remains unknown but some hypotheses were already raised: heredity - patients having relatives with the disease have a higher probability of developing the disease - and immune system malfunction. It is also believed that the interaction between genetic and environment factors may play a role in the aetiology of the disease. Factors such as stress and diet were considered possible causes for the disease but, in current days, as far as knowledge has advanced, it is known that these factors aggravate the disease but do not cause it [Latella et al., 2009, Cosnes et al., 2002]. Nonetheless, some factors have already being identified as risk factors for developing IBD [Cosnes et al., 2011] - Table 2.4.

Table 2.4: Risk factors for developing IBD

Factors	**Highest risk**
Age	Before 30 years old
Ethnicity	White race
Family history	Relatives with disease
Smoking habits	Cigarette smoking
Nonsteroidal anti-inflammatory medications	Increase the risk of disease or worse the disease
Place you live	Patient in urban area or industrialized country

IBD is a long course disease and can occur at any time of life, but about 80% of the diagnoses are made during the second and third decade of life [Vatn, 2009, Cosnes et al., 2011]. The clinical course is characterized by intermittent recurrences, and approximately 50% of patients have a mild course of the disease with a low prevalence of hospitalizations and other complications. The remaining patients have a more aggressive course and could require a more aggressive intervention, namely surgery [Cosnes et al., 2002, Vatn, 2009]. Being a chronic disease - for which medical, therapeutically and surgical therapies are not curative - patients need medical appoitments and may require hospital admission frequently. These factors create uncertainty about the future of patients with reflection in family relationship, professional and social life [Fauci et al., 2009, Baumgart and Sandborn, 2007]. The classical approach for IBD was to control the symptoms and only recently the target changed into an increase of the quality of life, reducing hospitalizations and surgeries so as to minimize the effects of the disease on daily activity, working capacity and the course of the disease [Devlin and Panaccione, 2010]. The course of the disease has become of particular importance since medical therapeutics can change the history of the disease, in particular with the introduction of biological therapy [Vermeire et al., 2007, Van Assche et al., 2010, Cosnes, 2009]. This way, identifying good prognostic models based on genetic/serological or clinical/demographic factors has been the focus of recent literature. However, the latter option seems more appealing since they are probability easier and faster to use since the data can be collected during daily clinical practice [Louis et al., 2010].

2.1.1 IBD in Portugal

In Portugal, only in the 80's were the first studies on the prevalence of CD made. Tavarela Veloso et al. presented in 1989 the first study for CD, with a cohort of patients between 1975 and 1988. This study was

based on clinical, radiological, endoscopical and histological data collected in several hospitals, presenting a prevalence of CD of 9.9 patients / 100000 inhabitants [Tavarela Veloso and Carvalho, 1989]. Some years later, Shivananda et al. developed an European multicentric prospective study, between 1991 and 1993, which included results for Portugal where the incidence rate ranged between 4.4 patients / 100000 inhabitant-years (in Braga) and 2.6 patients / 100000 inhabitant-years (in Almada), in the only two regions included in the study due to the nature of the study [Shivananda et al., 1996]. In 2009, Magro et al. developed a cross-sectional study to apply Montreal Classification to a large cohort of Portuguese patients with 5 or more years of the disease. In this work, it was possible to characterize patients from Portugal: 44% male, most of the patients between 17 and 40 years-old at diagnosis and with a median of 10 years (IQR 7-16) with the disease. Around 60% of the patients had a B1 phenotype in the first year and 34% presented ileal disease. Concernig severity, a minority if patients (less than 10%) did not receive steroids, immunossuppresants or were submitted to abdominal surgery.Twenty-seven percent of patients became steroid-dependent and 49% of then required immunosuppressants with or without biologic treatment [Magro et al., 2009]. In 2010, a pharmaco-epidemiological study approach to estimate the prevalence of the disease was published, where data from anti-inflammatory drugs consumption between 2003 and 2007 was used. The prevalence of CD increased from 42 (in 2003) to 71 patients / 100000 inhabitants (in 2007). Prevalence was always higher in women than men while, concerning age, the prevalence was higher in the 17-39 stratum (121 patients/100000 inhabitants) [Azevedo et al., 2010]. In 2014, the ECCO-EpiCom group conducted a new study where the incidence of the disease was shown to increase since the study of Shivananda, reaching an incidence rate of 7.0 patients / 100000 inhabitant-years, in the Vale do Sousa hospital [Burisch et al., 2014].

For ulcerative colitis (UC), the first study for an estimate of the prevalence of the disease was also made by Tavarela Veloso in 1995, a retrospective study which also included patients between 1975 and 1988 [Tavarela Veloso, 1995]. The estimated prevalence was 13.6 patients / 100000 inhabitants. Portuguese hospitals also collaborated with the EC-IBD study developed by Shivananda et al. with only two centers: one in the north of Portugal (Porto and Braga) and the other in the south (Lisboa and Almada). The incidence ranged between 1.7 and 5.5 patients / 100000 inhabitant-years, for south and north, respectively [Shivananda et al., 1996]. In 2009, Portela et al. developed a cross-sectional study to apply Montreal Classification in a large group of patients . Portuguese patients were more male (44%), with more left side colitis (52%), a median age at diagnosis was 38 years-old (± 15) and with a median of 8(± 8) years with the disease. The main complaints were rectal bleeding, diarrhea and abdominal pain. Sevem percent had family history of IBD and 8% were active smokers, 16% former smokers and 76% never smoked. Salicylates were used in almost 98% of the patients and in 38% were the only drug used in treatment. Sixty percent had taken steroids at least once, 14% immunosuppressors and 1% biologic agents. Concernig surgery arroud 5% of patietns were submitted to surgery mostly due to an acute severe flare or chronic relapsing disease [Portela et al., 2010]. In order to better estimate the prevalence of UC, the 2010 pharmaco-epidemiological study , using data from anti-inflammatory drugs consumption between 2003 and 2007, estimated an increase in UC prevalence from 43 to 73 patients / 100000 inhabitants. Prevalence was also always higher in women than men while, concerning age, the prevalence was higher for the 40-64 stratum (99 patients / 100000 inhabitants) [Azevedo et al., 2010]. In 2014, the ECCO-EpiCom group study presented an incidence of UC of 3.9 patients / 100000 inhabitant-years [Burisch et al., 2014].

A national study on the prevalence and incidence of both ulcerative colitis and Crohns disease is required, to better assess the need and impact of different early approaches, prognostic models, and patient follow-up at a national level.

2.2 Clinical decision

A clinical decision tool, as defined by Wyatt and Liu [Wyatt and Liu, 2002], is: *"any type of mechanical, paper, or electronic aid that collects or processes data from an individual patient and generates a specific output that aids clinical decision*". In this way, clinical decision tools are a kind of clinical decision support developed for a healthcare professional involved in patient care [Teich et al., 2005]. The definition of clinical decision support tools is nowadays a very important topic as they provide help in the diagnosis, prognosis or even treatment decisions [Lucas et al., 2004]. The interaction with the user can be classified according to three categories - presented in Table 2.5 - and different users also imply different usage risks - Table 2.6 [Musen et al., 2006].

Table 2.5: Classification of clinical decision support according interaction

Level	
Passive	help in decision making but without recommendation or suggestions
Active	with suggestions and/or explicit actions
Cooperative	allowing the user to modify or redefine the recommendation or decision

Table 2.6: Classification of different usage risk for clinical decision support

Level	
Low	if the user is a health care professional, hence providing knowledgeable control
High	if the user is a patient or the general public
Very high	if no human user is in control

In clinical decision it is absolutely necessary the use of all available evidence, which includes the physicianś personal experience, the aggregate evidence included in quality clinical research and, not less important, the values, needs and expectations of each patient [Sackett et al., 1996]. But all these data and information come with uncertainty: uncertainty in the observed patients (information collected from a sample), uncertainty in collected data (precision or random error, and validity or systematic errors), uncertainty in the applied methods (data processing and data analysis, confounding bias), uncertainty in the chosen knowledge representation (level of abstraction), uncertainty in the generalization procedure (from a model to each patient) and, finally, uncertainty in the actual decision applied to the patient. But in what way can we help the decision making? The crucial step is formalizing the uncertainly in order to reduce it [Rodrigues, 2016]. Therefore, it is necessary to use robust methods which can comply with this concept.

Traditionally, in prognostic or diagnostic models, support systems are based in logistic or linear regression [Campbel, 2001, Lucas, 2004]. These techniques have the advantage of being easily interpretable from the

clinical point of view, having nonetheless a poor graphical representation. The nature of biomedical data requires the application of techniques that go beyond traditional biostatistics [Lucas, 2004] , such as Bayesian networks (which allow the computation of posterior probabilities) [Darwiche, 2010] or decision trees (whose estimates are computed strictly from the proportions in the sample) [Breiman et al., 1984]. Both techniques have an intuitive graphical representation for the user without losing the necessary formalism to clinical reasoning.

For learning these methods it is important to follow several steps, which include selection of relevant variables, identification of variables interaction, validation of the model and sensitivity analysis. In each of them it is necessary to take into account the knowledge of experts, the evidence in the literature and not least important the patient data [Lucas et al., 2004, Lucas, 2004].

2.2.1 Bayesian network

Contrary to the common frequentist statistical inference, which gives us confidence intervals and hypothesis testing theory, Bayesian statistical approaches compute the probability that the hypothesis is true, updating the prior probability about the hypothesis with the new incoming available data [Petrie and Sabin, 2009]. In medical diagnosis problems, it is common to calculate estimates such as prevalence (prev) of the disease (prior probability) and sensitivity (sens) or specificity (spec) of a diagnostic test, equivalent to the conditional probability of positive/negative test given the presence/absence of disease - e.g $sens = p(+|D) = P(+, D)/P(D)$. But in daily routine what is important to be calculated is the probability of having a disease given a positive/negative test. This value is the positive/negative predictive value (posterior probability) and can be easily calculated using Bayes theorem:

$$p(D|+) = \frac{p(+, D) * p(D)}{p(+)} \tag{2.1}$$

with

$$p(+) = p(+|D) * p(D) + p(+| \sim D) * p(\sim D) \tag{2.2}$$

where D is the disease outcome and $+$ is the observation of a positive test. Given the usual information available for the diagnostic test and the disease, this equation could be re-written as:

$$p(D|+) = \frac{sens * prev}{sens * prev + (1 - spec) * (1 - prev)} \tag{2.3}$$

For example, considering a disease with a prevalence of 1%, and a test with 99% sensitivity and 60% specificity, the question is what is the probability of having the disease given a positive test? If we apply the previously presented Bayes theorem to calculate p(D|+), i.e. the positive predictive value, we obtain the following posterior probability:

$$p(D|+) = \frac{0.001 * 0.99}{0.001 * 0.99 + 0.99 * 0.40} = 0.02 \tag{2.4}$$

showing that the probability of disease has increased to 2% after the observation of a positive test. Graphically, this association can be visualized as a directed graph, as depicted in Figure 2.1.

But, usually, a disease does not have only one symptom or observable expression. So it is necessary to develop models which allow the presence of many characteristics that could explain the outcome. If we have a patient with two tests (symptoms) and we want to compute the updated posterior probability of having a disease, the graphical model needs to be extended as in Figure 2.2.

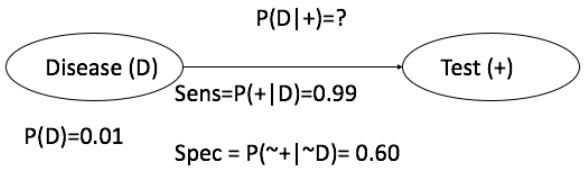

Figure 2.1: Graphical probabilistic model for representation of a diagnostic test

Using the same factorization as before the $p(D, +_1, +_2)$ is calculated as follows:

$$p(D|+_1,+_2) = \frac{p(D,+_1,+_2)}{p(+_1,+_2)} = \frac{p(+_1|D)*p(+_2|D)*p(D)}{p(+_1|D)*p(+_2|D)*p(D)+p(+_1|\sim D)*p(+_2|\sim D)*p(\sim D)} \quad (2.5)$$

Again this equation could be re written using the measures calculated for both tests and the information about the prevalence of the disease:

$$p(D|+_1,+_2) = \frac{sens_1 * sens_2 * prev}{sens_1 * sens_2 * prev + (1-spec_1) * (1-spec_2) * (1-prev)} \quad (2.6)$$

With more than two tests (variables) the problem becomes more complex and requires robust algorithms to deal with all the involved data, but the formalism lingers.

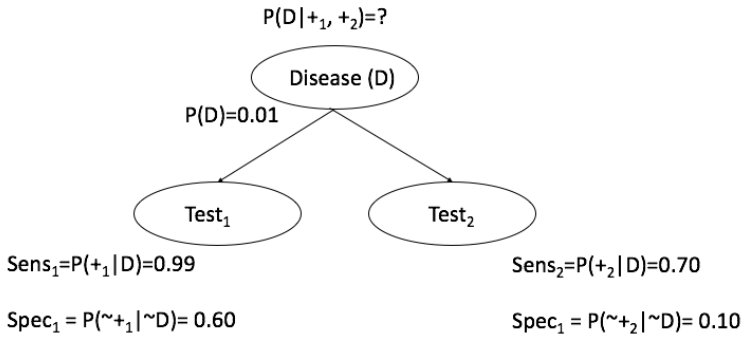

Figure 2.2: Graphical probabilistic model for representation of two diagnostic tests

Given its graphical representation and statistical foundations, this modelling is known as Bayesian networks [Darwiche, 2010]. Generically, a Bayesian network represents a joint distribution of a set of variables, specifying the independence assumption between each pair of variables. This dependence is representing by a direct acyclic graph, where each variable is represented by a node. An arc in the network shows that the descendant variable is conditionally dependent of the ascendant node [Mitchell, 1997]. This representation of knowledge includes two distinct models: a qualitative model, which represents the relationships among variables, and a quantitative model, the joint probability distribution represented by the conditional probabilities (further explained). The simpler Bayesian network is the nave Bayes (NB) - Figure 2.3. This model assumes that all variables are independent among themselves, and conditionally independent given the outcome [Domingos and Pazzani, 1997].

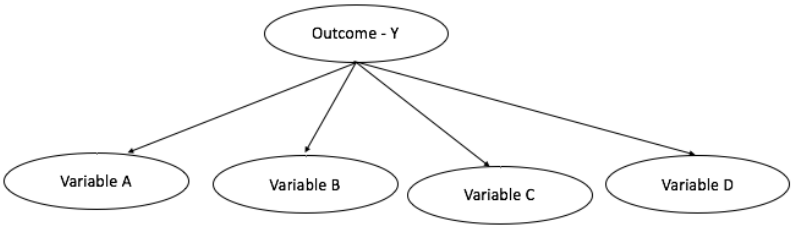

Figure 2.3: Qualitative model for Naïve Bayes

In order to give expression to the relations among variables it is important to define the quantitative model, i.e. the joint probability of the variables which can be computed using the following equation:

$$p(V_1, ...V_n) = \prod_{i=1}^{n} p(V_{i|}Pa_i) \tag{2.7}$$

where $V_1, ..., V_n$ are a set of variables and Pa_irepresents the set of ascendant nodes of i. For simple networks, this joint probability is easily computed. For the example in Figure 2.3 the joint probability for the outcome y is given by:

$$p(Y, A, B, CD) = p(Y) * p(A|Y) * p(B|Y) * p(C|Y) * p(D|Y) \tag{2.8}$$

But in real world variables are not independent, rather related among them. To allow such interaction, Friedman et al. [Friedman et al., 1997] developed an adaptation of nave Bayes: the Tree Augmented Nave Bayes (TAN), an example of which is represented in Figure 2.4. The TAN classifier model includes two assumptions: 1) all explanatory variables are conditioned by the outcome, i.e. all will directly influence the outcome during inference; and 2) an optional additional dependence is allowed for each variable, i.e. each variables effect might be adjusted by one additional covariable [Huang et al., 2002]. From those, the method allows learning the network structure from the data [Lucas, 2004, Mitchell, 1997] aiming at finding the structure that best fits the available data and which may provide the best classifier for the designated outcome.

For this example, the joint probability has now the following formulation:

$$p(Y, A, B, C, D) = p(Y) * p(A|Y) * p(B|Y) * p(C|Y) * p(D|Y, C) \tag{2.9}$$

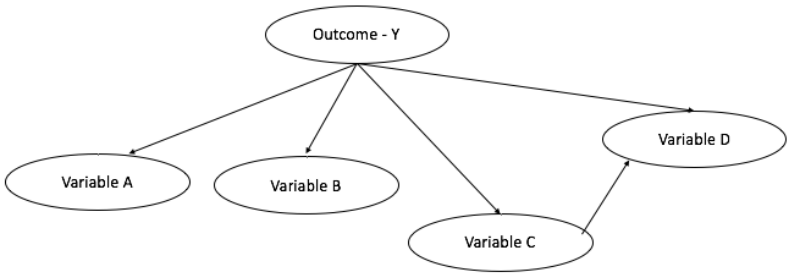

Figure 2.4: Qualitative model of a TAN Classifier

Several different topologies and learning algorithms exist, but the TAN has given solid evidence of providing sound classifiers [Dias et al., 2014, Sakellaropoulos and Nikiforidis, 2000] and knowledge representations in clinical settings.

Bayesian approaches have an extreme importance in clinical problems, since they provide a qualitative and quantitative perspective. Additionally, they take into account prior knowledge, making data analysis an update processing of prior knowledge with observed evidence [Lucas, 2004], making it a very useful tool in the practice of evidence-based medicine.

2.2.2 Decision tree

A decision tree is a formal knowledge model which uses a divide-and-conquer strategy to solve decision problems. A complex problem is divided in simpler problems to which the same strategy is applied, recursively. The solution of sub-problems can afterwards be combined, in the form of a tree, to produce the solution of the original problem. One advantage of this approach relates with its capacity to divide the instance space into disjoint subspaces, possibly adjusting different models to each subspace. As other knowledge models, decision trees are commonly handcrafted by experts. But this idea of defining subspaces allows the rising of automatic methods to induce the trees from data, and is the basis of all algorithms behind decision tree induction, such as: ID3 [Quinlan, 1986], which can use the entropy or the information gain to choose the best variable to be selected at each node; CART [Breiman et al., 1984], which uses the entropy (a negative sum of logarithmic proportions) to choose the best variable to be selected at each node; or CHAID [Kass, 1980], which uses a chi-squared test, with Bonferroni correction, instead.

Formally, a decision tree is a direct acyclic graph where each node has exactly one ascendant, wherein each node could be a splitting node or a leaf node (an example is presented in figure 2.5). In splitting nodes, a conditional test is applied based on the values of a single variable (selected for this node). In leaf nodes, the outcome variable within the instance subspace, defined by ascendant splits, is inspected to form a decision (usually, the majority class within the corresponding subspace is used as predicted class).

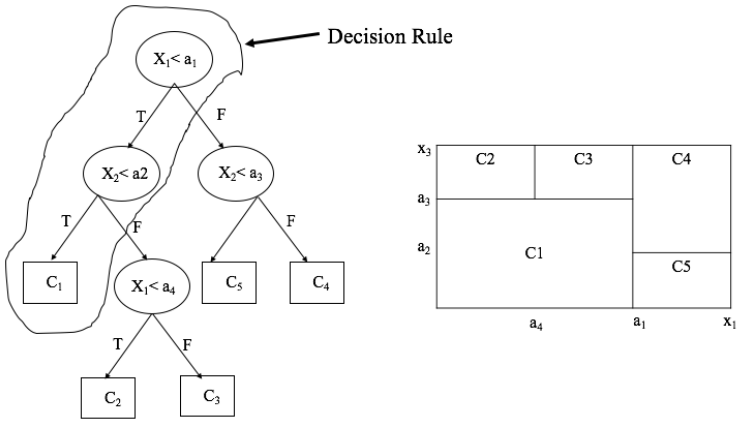

Figure 2.5: Decision tree example (adapted from [Gama et al., 2012])

Figure 2.5 represents an example of a decision tree and the correspondent split in the space of variables x_1 and x_2. Each node of the tree corresponds to a subspace defined by the variables. The areas defined by the leaves of the tree are mutually exclusive and the union of these areas is the entire instance space. This way defined, each path traversing the tree defines a decision rule (e.g. if $x_1 < a_1$ <x1 and then $C1$).

2.2.3 Methods of validation

After the development of any model, it is necessary to estimate the performance of the model. In fact, the generalising ability of the model is related to its capacity to predict cases on an independent sample of new data [Hastie et al., 2001]. Therefore, the aim of this approach is to estimate the validity of the model by assessing the expected error associated to it. There are many methods to estimate this validity, as presented as follows:

Independent external sample to use an independently collected sample of data and compute the predictive error in it;

Holdout to divide the data into two samples: one used for building the model and the other to compute the predictive error;

Cross-validation to divide the sample into k exclusive sets of equal size (folds) and assess validity in k models, each built with k-1 folds and tested in the remaining fold, with the error estimated as the mean of all k error estimates - this is usually repeated several times to improve the precision of the error estimates;

Leave-one-out a special case of cross-validation, where k=n, with n being the number of cases in the sample.

In classification problems, the most common procedure to validate the models is the confusion matrix which allows the comparison between the result of the model (prediction) and the real result - Table 2.7. This matrix allows also the computation of many other measures, commonly used in diagnostic studies - Table 2.8.

Table 2.7: Diagnostic testing confusion matrix

	Real		
	Positive	Negative	Total
Result of test			
Positive	TP	FP	TP+FP
Negative	FN	TN	FN+TN
Total	TP+FN	FP+TN	n

TP: True positive, TN: True negative,
FP: False positive, FN: false negative

Many classifiers (likewise, diagnostic tests) provide a continuous result rather than a class outcome. For these, if no cut-off is previously defined (which can translate a continuous value into a class outcome), another way to evaluate classifiers is to construct and analyse a receiver operating characteristics curve (ROC), which assesses the discriminative power of the models. This curve allows the visualization of the relation between sensitivity and specificity of the model, for each possible cut-off value, enabling either the selection of an optimal (according to the study aims, as described further down) cut-off point or the evaluation of the classifier as a whole - Figure 2.6. Having into account the expected prevalence of the outcome and the impact of a

Table 2.8: Descriptions of measures which can be calculated from the confusion matrix (using the diagnostic testing metaphor)

Measure	Acronym	Description	Formula
Pre-test probability	pretest	Prevalence	TP/n
Pre-test odds	pretest odds		$pretest/(1-pretest)$
Accuracy	acc	Proportion of cases correctly classified	$(TP+TN)/n$
Sensitivity	sens	Proportion of patients with the disease who had a positive test	$TP/(TP+FN)$
Specificity	spec	Proportion of patients without the disease who had a negative test	$TN/(TN+FP)$
Positive predictive value	PPV	Proportion of patients with positive test who actually have the disease	$TP/(TP+FP)$
Negative predictive value	NPV	Proportion of patients with negative test who actually do not have the disease	$TN/(TN+FN)$
Positive likelihood ratio	LR+	Ratio between the probability that a test is positive in disease patients and the probability that test is positive in non-disease patients	$sens/(1-spec)$
Negative likelihood ratio	LR-	Ratio between the probability that a test is negative in disease patients and the probability that test is negative in non-disease patients	$(1-sens)/spec$
Positive post-test odds		Odds of disease after a positive test	$pretest\ odds * LR+$
Negative post-test odds		Odds of disease after a negative test	$pretest\ odds * LR-$

positive/negative prediction, the cut-off can be chosen following either a rule-in approach (aiming at a high positive predictive value) or a rule-out approach (aiming at a high negative predictive value) instead of the balanced approach where both sensitivity and specificity are optimized together.

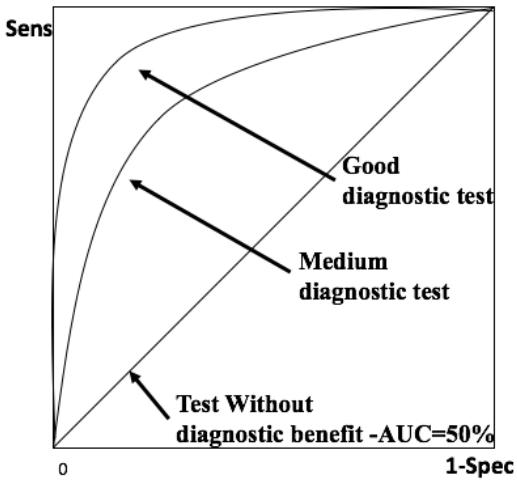

Figure 2.6: Examples of ROC curves of different quality models.

Associated with this representation is the computation of the Area Under the Curve (AUC). This metric varies between 0 and 1 and can be interpreted as the probability that the model would rank a randomly chosen positive case higher than one other randomly chosen negative case.

2.2.4 From modeling to bedside

The application of classifiers to actual patients creates the need to translate the resulting probabilities of the outcome into an actionable decision. Therefore, the visualization of modeling results is of major importance to enable their use at bedside; possible means include:

- The classifier **result** (either a continuous value, such as a probability, or a class outcome) can be directly shown to the human and interpreted as extra evidence to be combined with other sources of evidence for the actual patient;
- **Graphical models** (such as Bayesian networks and decision trees) allow a deeper understanding of the relations among factors and can even allow a cooperative interaction with the human (e.g. to assess the impact of different observed signs or symptoms in the classifiers result);
- By defining **risk matrices**, which create subgroups of patients with similar characteristics (usually based upon 2 to 4 variables) for which risk estimates are presented; the human user can then easily allocate the patient to one of the subgroups and use the aggregated risk estimate as evidence in their decision making process. In order to choose which variables should define the subgroups in a risk matrix, different methods can be used to assess factor relevance, or they can be chosen by clinical relevance.

3. Objectives

3. Objectives

This thesis has three main goals:

Goal 1: Evidence (Chapter 4)

The first aim of this thesis is to summarize the evidence regarding Crohn's disease and ulcerative colitis outcomes and corresponding associated factors, limited to clinical and demographical data.

Goal 2: Classification (Chapter 5)

The second aim of this thesis is to identify and assess risk factors for outcomes identified in Goal 1 for Crohn's disease, using an independent cohort of patients.

Goal 3: Prediction (Chapter 6)

The third aim of this thesis is to develop and validate prognostic models for outcomes identified in Goal 1, with risk factors isolated in Goals 1 and 2.

4. Evidence

4. Evidence

The first aim of this thesis is to summarize the evidence regarding Crohn's disease and ulcerative colitis outcomes and corresponding associated factors, limited to clinical and demographical data. Factors such as age at diagnosis, perianal disease, initial use of steroids and disease location were identified as independent factors of disabling disease for Crohn's patients. Concerning ulcerative colitis, gender, smoking habits, disease extent, need for corticosteroids and hospitalization were associated with colectomy.

Two studies were conducted:

Prognostic factors for disabling Crohn's disease: a systematic review and meta-analysis.
World Journal of Gastroentereology 19(24): 3866-71, 2013.
Cláudia Camila Dias, Pedro Pereira Rodrigues, Altamiro da Costa Pereira, Fernando Magro

Clinical Predictors of colectomy in patients with ulcerative colitis: systematic review and meta-analysis of cohort studies.
Journal of Crohn's and Colitis, 9(2): 156-163, 2015
Cláudia Camila Dias, Pedro Pereira Rodrigues, Altamiro da Costa Pereira, Fernando Magro

4.1 Prognostic factors for disabling Crohn's disease: a systematic review and meta-analysis

World Journal of Gastroentereology 19(24): 3866-71, 2013.

Cláudia Camila Dias, Pedro Pereira Rodrigues, Altamiro da Costa Pereira, Fernando Magro

4.1. PROGNOSTIC FACTORS FOR DISABLING CROHN'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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META-ANALYSIS

Clinical prognostic factors for disabling Crohn's disease: A systematic review and meta-analysis

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Abstract

AIM: To identify demographic and clinical factors associated with disabling Crohn's disease (CD).

METHODS: A systematic review and meta-analysis of observational studies, focusing on the factors that can predict the prognosis of different outcomes of CD was undertaken. PubMed, ISI Web of Knowledge and Scopus were searched to identify studies investigating the above mentioned factors in adult patients with CD. Studies were eligible for inclusion if they describe prognostic factors in CD, with inclusion and exclusion criteria defined as follows. Studies with adult patients and CD, written in English and studying association between clinical factors and at least one prognosis outcome were included. Meta-analysis of effects was undertaken for the disabling disease outcome, using odds ratio (OR) to assess the effect of the different factors in the outcome. The statistical method used was Mantel-Haenszel for fixed effects. The 16-item quality assessment tool (QATSDD) was used to assess the quality of the studies (range: 0-42).

RESULTS: Of the 913 papers initially selected, sixty studies were reviewed and three were included in the systematic review and meta-analysis. The global QATSDD scores of papers were 18, 21 and 22. Of a total of 1961 patients enrolled, 1332 (78%) were classified with disabling disease five years after diagnosis. In two studies, age at diagnosis was a factor associated with disabling disease five years after diagnosis. Individuals under 40 years old had a higher risk of developing disabling disease. In two studies, patients who were treated with corticosteroids on the first flare developed disabling disease five years after diagnosis. Further, perianal disease was found to be relevant in all of the studies at two and five years after diagnosis. Finally, one study showed localization as a factor associated with disabling disease five years after diagnosis, with L3 being a higher risk factor. This meta-analysis showed a significantly higher risk of developing disabling disease at five years after initial diagnosis among patients younger than 40 years of age (OR = 2.47, 95%CI: 1.74-3.51), with initial steroid treatment for first flare (OR = 2.42, 95%CI: 1.87-3.11) and with perianal disease (OR = 2.00, 95%CI: 1.41-2.85).

CONCLUSION: Age at diagnosis, perianal disease, initial use of steroids and localization seem to be independent prognostic factors of disabling disease.

Key words: Crohn's disease; Disabling disease; Prognostic factors; Outcome; Systematic review; Meta-analysis

Dias CC, Rodrigues PP, da Costa-Pereira A, Magro F. Clinical prognostic factors for disabling Crohn's disease: A systematic review and meta-analysis. *World J Gastroenterol* 2013; 19(24): 3866-3871 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i24/3866.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i24.3866

INTRODUCTION

Crohn's disease (CD) occurs in equal proportion in both genders and its incidence has been growing worldwide in the last decades[1]. CD is a disabling disease affecting psychological, familial, and social dimensions of life[2]. Therefore, the need to develop a specific instrument able to evaluate disabilities and identify specific factors as predictors is paramount. This is particularly true since in the last decades the medical treatment options have been dramatically changed. Other strategies are now approaching, namely accelerate step-up and top-down treatment[3]. The top-down strategy is based on the very early use of intensive therapy (immunosuppressants and/or biologics) to maintain a good quality of life from the first flare-up of the disease and prevent any irreversible consequences[3]. Therefore, it is now crucial to identify simple clinical criteria at diagnosis to predict CD outcome. This work aims to systematically review the evidence with respect to predictive clinical prognostic factors for CD.

MATERIALS AND METHODS

A systematic review and meta-analysis of observational studies focusing on the factors that can predict the prognosis of different outcomes of CD was undertaken. The methodology included the definition of eligibility criteria, search strategies, study selection and characteristics, outcome measures, quantitative data synthesis and sensitivity analysis, methodological quality of studies, and statistical data analysis.

Eligibility criteria

Studies that described prognostic factors in CD were eligible for inclusion. The criteria for inclusion were studies with adult patients and CD written in English and studying association between clinical factors and disabling disease. Studies not in English, without available abstract, with genetic or serologic factors, biomarker studies, or those addressing diagnosis or quality of life were excluded.

Search strategy

The main method to search for the eligible articles was a broad literature search using PubMed with the following keywords and MeSH terms: *"crohn disease"[MeSH Terms] OR "crohn"[All Fields] AND predictor [All Fields] OR predictors [All Fields] OR predict [All Fields] OR "prognostic factor" [All Fields] OR "prognostic factors" [All Fields]*. Literature searches were also undertaken in Scopus database and ISI Web of Knowledge using the same search keywords: *crohn disease AND (predictors OR predict OR prognostic factors)*.

Study selection

The studies were screened and selected by two reviewers. First, all titles and abstracts were read and the inclusion and exclusion criteria were applied. Second, the reviewers read the full text of all papers considered for inclusion after abstract selection, again applying the inclusion and exclusion criteria.

Study characteristics

The following properties of each study were recorded: total number of patients, prognostic variables, and percentage of patients with disabling disease.

Outcome measures

The aim of the study is to assess prognostic factors to predict disabling CD.

Methodological quality of included studies

The 16-item quality assessment tool (QATSDD), developed by Higgins *et al*[4], was used to assess the quality of the included studies. This tool includes 16 items, scored between 0 and 3, and can be applied to different types of studies using different approaches. However, two of the items were not evaluated as they only address qualitative studies, hence we only considered a maximum score of 42.

Statistical analysis

Statistical evidence of effects is presented as described in the original studies. Meta-analysis of effects was undertaken for the disabling disease outcome using odds ratio (OR) to assess the effect of the different factors in the outcome. The statistical method used was Mantel-Haenszel for fixed effects. All included estimates are recomputed from original articles descriptions, potentially resulting in slightly different values. All reported *P*-values are 2-sided with a significance level of 5%. Statistical heterogeneity was assessed with the I^2 statistic; values higher than 50% indicate a substantial level of heterogeneity[5]. RevMan v5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2011) was used to calculate OR and 95%CI for disabling disease and to derived forest plots showing the results of individual studies and pooled analysis.

RESULTS

Search and study selection

A total of 913 articles were identified using the search

4.1. PROGNOSTIC FACTORS FOR DISABLING CROHN'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Table 1 Characteristics of the studies

Ref.	Country	Sample size (*n*)	Type of study	Disabling	Follow-up (yr)	Factor	QATSDD
Beaugerie *et al*[6]	France	1123	Retrospective	85.2%	5	Age (under 40 yr) Steroids for 1st flare Perianal disease	22
Loly *et al*[7]	Belgium	361	Retrospective	57.9%	5	Steroids for 1st flare Perianal disease L3	18
Yang *et al*[8]	China	207	Retrospective	71.0%	2	Steroids for 1st flare Perianal disease	21
				80.2%	5	Age (under 40 yr)	

QATSDD: Sixteen-item quality assessment tool.

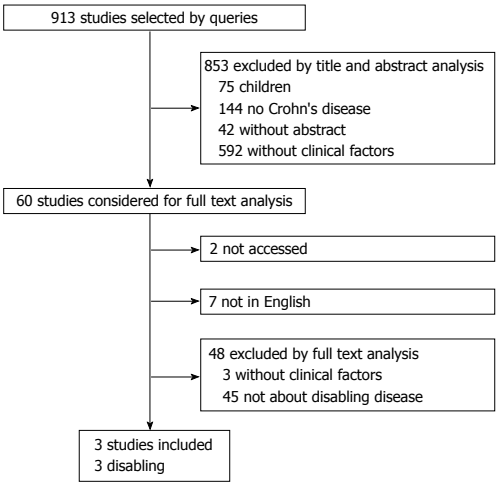

Figure 1 Flowchart of the selection process for this meta-analysis.

strategy. After reading all titles and abstracts, 853 articles were excluded (Figure 1). Sixty studies were reviewed in detail and three articles were included in the study. A new search of the literature focused on the outcome was made in order to find other papers that could have been missed by the generic search. The global QATSDD scores ranged between 18 and 22. The main characteristics of the studies are summarized in Table 1.

Predicting factors of disabling disease

Beaugerie *et al*[6] and Loly *et al*[7] define disabling disease by the presence of at least one of the following criteria: two steroid courses required and/or steroid dependency; further hospitalization after diagnosis for flare up or complications of the disease; chronic symptoms (diarrhea with nocturnal and/or urgent stools, intensive abdominal pain due to intestinal obstruction, fever, fatigue attributable to the disease); joint pain; painful uveitis or pyoderma gangrenous for 12 mo within the five year study; immunosuppressive therapy and intestinal resection or surgical operation for perianal disease. Yang *et al*[8] defined CD as disabling if patients satisfy at least one of the following criteria: require two or more steroids courses and/or steroid dependency; need immunosuppressive therapy; intestinal resection or surgical operation for perianal disease and hospitalization after diagnosis for the treatment of acute exacerbation, or complication of the disease.

According to Beaugerie *et al*[6], 957 of 1123 patients (85.2%) were classified with disabling disease. With a sample of 361 patients, Loly *et al*[7] found 209 patients (57.9%) with disabling disease, while Yang *et al*[8] found 80.2% of 207 patients with disabling disease five years after diagnosis, and 71% of patients already had disabling disease two years after diagnosis.

Different factors were found that could predict disabling disease, namely age at diagnosis, use of steroids, perianal disease, and localization.

Age at diagnosis

Beaugerie *et al*[6] found age at diagnosis as a factor associated with disabling disease. Patients less than 40 years old had a higher risk of developing disabling disease than older patients (OR = 2.1, 95%CI: 1.3-3.6) five years after the diagnosis. Yang *et al*[8] also showed that patients under 40 had a higher risk of developing disabling disease (OR = 3.56, 95%CI: 1.74-7.30).

Results of studies comparing younger patients (under 40) with older patients (over 40) are shown in Figure 2A. A fixed effects model shows that younger patients had a higher risk of disabling disease five years after diagnosis (OR = 2.47, 95%CI: 1.74-3.51). There was no evidence of statistical heterogeneity among the studies (I^2 = 26%).

Steroids for treatment of first flare

Both Beaugerie *et al*[6] and Loly *et al*[7] show patients who had initial requirement of steroids for treating the first flare had a higher risk of developing disabling disease five years after diagnosis when compared to those who did not require treatment (OR = 3.1, 95%CI: 2.2-4.4 and OR = 1.7, 95%CI: 1.02-2.7, respectively). Yang *et al*[8] found similar results two years after diagnosis (OR = 2.142, 95%CI: 1.068-4.298).

Results of these different studies comparing patients with and without steroid requirement treatment are presented in Figure 2B. A fixed effects model shows that patients with steroid treatment had a higher risk of disabling

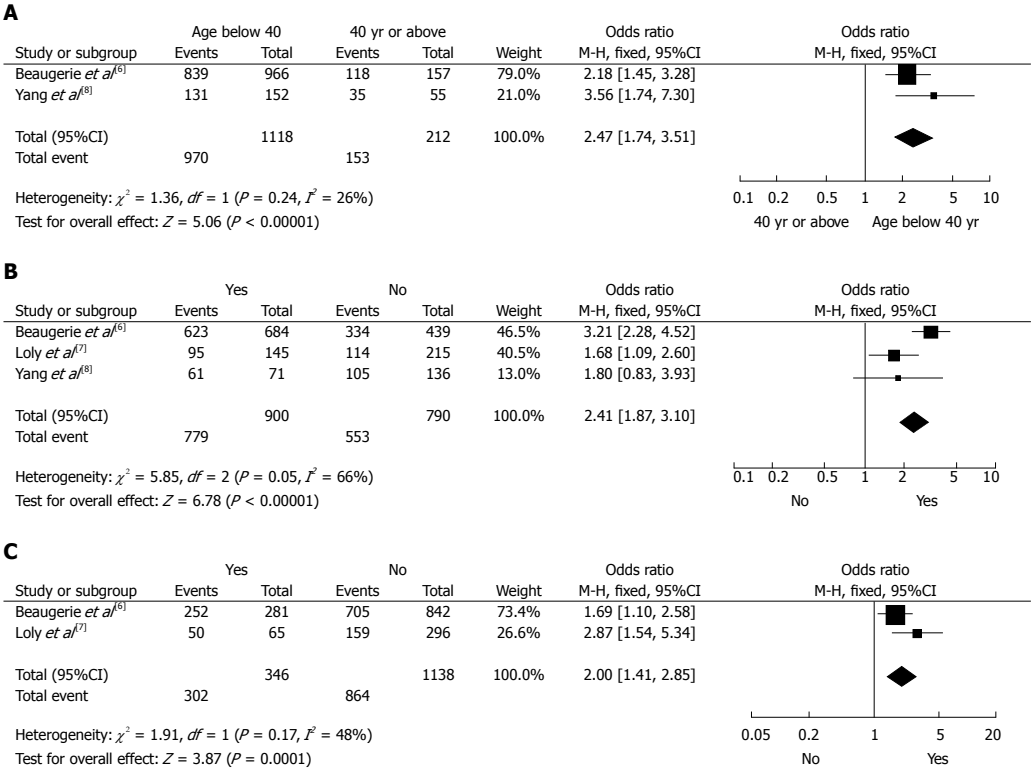

Figure 2 Predictor of disabling disease. A: Age at diagnosis as a predictor of disabling disease; B: The use of steroids for treatment of the first flare as a predictor of disabling disease; C: Perianal disease as a predictor of disabling disease.

disease five years after diagnosis (OR = 2.41, 95%CI: 1.87-3.10). Significant heterogeneity was found among the studies (I^2 = 66%). Nevertheless, all studies found a higher risk of disabling disease for patients on steroids.

Perianal disease

In all three studies, patients with perianal disease had a higher risk of developing disabling disease five years after diagnosis when compared to patients without perianal disease: Beaugerie *et al*[6] (OR = 1.8, 95%CI: 1.2-2.8), Loly *et al*[7] (OR = 2.6, 95%CI: 1.4-5.1), Yang *et al*[8] (two years after diagnosis) (OR = 5.433, 95%CI: 1.585-18.620).

The comparison between patients with and without perianal disease is shown in Figure 2C. A fixed effects model shows the presence of perianal disease as a high risk of disabling disease five years after diagnosis (OR = 2.00, 95%CI: 1.41-3.85). There was no evidence of statistical heterogeneity among the studies (I^2 = 48%).

Localization

One study associated disabling disease to the localization of the disease. In this study, patients with L3 localization had a higher risk of developing disabling disease five years after the diagnosis (OR = 1.74, 95%CI: 1.06-2.8)[7].

DISCUSSION

CD is a chronic disease with no known medical or surgical cure, requiring several appointments and hospitalizations for those afflicted. There are several reasons stressing the importance of prognostic factors: (1) Recent available drugs, namely anti-tumour necrosis factor (TNF), having the potential of inducting mucosal healing and prolonged clinical remission; (2) Mucosal healing has been considered a therapeutic goal; and (3) Early therapeutic interventions are followed by a better outcome. Therefore, it is imperative that therapeutic options are optimized.

The present systematic review and meta-analysis presented some of the factors that could help clinicians identify risk groups for disabling CD. Age, perianal disease, the use of steroids and localization were all associated with disabling disease. Although other markers can help clinicians to predict disease course of CD, namely genetic, serologic and endoscopic findings, we limited this meta-analysis to demographic and clinical characteristics due to feasibility to apply at diagnosis at the bedside.

Three studies address disabling disease and used similar definitions, although in Yang *et al*[8] the presence of chronic symptoms like diarrhea, fever, fatigue, was not

considered. All studies were retrospective and the number of patients in each study ranged from 207 to 1123[6,8]. It was clear that a large number of patients had disabling disease (range: 59%-81%), which gives an indication of the severity of the disease. Moreover, the study with the highest percentage of disabling disease included the least amount of defining characteristics[8]. Our meta-analysis showed that patients under 40 years old and patients with an initial requirement of steroids, or patients with perianal disease had a higher risk of having disabling disease five years following initial diagnosis. These results are in line with the three studies used in the meta-analysis[6-8]. Although the definition of disabling disease in Yang *et al*[8] is slightly different, this study had a lower weight in the final result of the meta-analysis, hence limiting the possible bias. Even though the effect of age at diagnosis was clear in the meta-analysis; further studies are necessary to better assess relative CD risk, including an evaluation of more patients diagnosed after the age threshold. We call into question some of the recent points included in disability definition, namely steroids following the first flare, the need for immunosuppressants, and surgery. The percentage of patients treated with steroids in the first flare (65%) in Beaugerie *et al*[6] was very similar to the percentage of patients who received steroids within in the first year of disease in the North-European population-based study, however this only reflects the step-up strategy, and the population on immunosuppressants was very low[9]. Markowitz *et al*[10] showed children requiring steroids for the treatment of the first flare-up that a very early use of 6-Mercaptopurine was associated with steroid sparing and a more favorable clinical outcome in the 18-mo period following diagnosis. Similar results were observed in those treated with anti-TNF in the first two years of disease[11]. Finally, the role of early surgery in limiting ileal disease with regard to CD prognosis is also debatable. In conclusion, the risk factors analyzed in this meta-analysis should be considered when new scores or approaches are taken concerning risk factors in CD outcome, particularly when more early therapeutic approaches are imminent.

The QATSDD scale, developed by Sirriyeh *et al*[5], allows the comparison of the quality of the included papers even when their designs are different. The included papers consistently presented low quality scores, especially considering the representativeness of the sample and the absence of a critical discussion of strengths and limitations.

The results of this study may need further confirmation due to the small number of reviewed studies and their low quality (maximum QATSDD score of 22 out of 42). Nevertheless, this work presents a step-forward in the definition of clinical predictors for disabling CD, exposing their relevance and impact in disease prognosis.

In summary, this review and meta-analysis showed that age, perianal disease and the use of steroids are associated with disabling disease. The use of these factors in building predictive models for CD prognosis could enhance the initial clinical approach, and therefore improve the clinical outcome of patients with severe disease. However, more elaborate and precise definitions of disabling and severe disease are needed.

COMMENTS

Background

Crohn's disease (CD) occurs in equal proportion in both genders and its incidence has been growing worldwide in the last decades. CD is a disabling disease affecting psychological, familial, and social dimensions of life. Therefore, the need to develop a specific instrument able to evaluate disabilities and identify specific factors as predictors is paramount.

Research frontiers

The top-down strategy is based on the very early use of intensive therapy (immunosuppressants and/or biologics) to maintain a good quality of life from the first flare-up of the disease and prevent any irreversible consequences. Therefore, it is now crucial to identify simple clinical criteria at diagnosis to predict CD outcome.

Innovations and breakthroughs

This work aims to systematically review the evidence with respect to predictive clinical prognostic factors for CD.

Applications

This review and meta-analysis showed that age, perianal disease and the use of steroids are associated with disabling disease. The use of these factors in building predictive models for CD prognosis could enhance the initial clinical approach, and therefore improve the clinical outcome of patients with severe disease. However, more elaborate and precise definitions of disabling and severe disease are needed.

Peer review

It is one of the first work searching the role of CD in disability of the patient. The authors performed an extensive review of multiple manuscript related with the topic. The manuscript is very well prepared and written and can be accepted for publication.

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4.2 Clinical predictors of colectomy in patients with ulcerative colitis: systematic review and meta-analysis of cohort studies

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Original Article

Clinical Predictors of Colectomy in Patients with Ulcerative Colitis: Systematic Review and Meta-analysis of Cohort Studies

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Abstract

Introduction: Colectomy is a major event that may significantly affect the outcome of ulcerative colitis (UC) in terms of both quality of life and mortality. This paper aims to identify clinical prognostic factors that may be significantly associated with this event.
Methods: PubMed, ISI Web of Knowledge and Scopus were searched to identify studies investigating the association between clinical factors in adult patients with UC and studied events. The clinical factors evaluated in this meta-analysis were gender, smoking habits, disease extent, use of corticosteroids, and episodes of hospitalization.
Results: Of the 3753 initially selected papers, 20 were included. The analysis showed a significantly lower risk of colectomy for female patients (odds ratio [OR] 0.78 [95% CI 0.68, 0.90]) and for smoking patients (OR 0.55 [0.33, 0.91]), and a higher risk for patients with extensive disease (OR 3.68 [2.39, 5.69]), for patients who took corticosteroids at least once (OR 2.10 [1.05, 4.22]), and for patients who were hospitalized (OR 4.13 [3.23, 5.27]).
Conclusion: Gender, smoking habits, disease extent, need for corticosteroids, and hospitalization were all significantly associated with UC prognosis. These results may clarify the relative influences of these and other prognostic factors in the natural course of the disease and therefore help improve the management approach, thus improving the follow-up of patients.

Keywords: Ulcerative colitis; clinical prognosis; prognostic factors; outcome; systematic review; meta-analysis

1. Introduction

Ulcerative colitis (UC) has a heterogeneous course. It is a chronic disease in which activity has been described as mild, moderate, or severe, based on how many of the following symptoms are present: bloody diarrhea, abdominal cramps, and fever.[1] Medical treatment and surgery are the two possible treatment options. The primary goal of medical treatment is to reduce symptoms, but nowadays it is also aimed at clinical, endoscopic, and histologic remission. Surgery is limited to refractory patients and to those with dysplasia or carcinoma.[2,3] Therefore, it is now crucial to define clinical criteria at diagnosis to help predict UC outcome. Demographic and clinical characteristics are also important since they are easy to use and have been consistently associated with the disease course.[4] This work aims to systematically review the evidence with respect to predictive clinical prognostic factors for UC.

4.2. CLINICAL PREDICTORS OF COLECTOMY IN PATIENTS WITH ULCERATIVE COLITIS: SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

2. Materials and Methods

A systematic review and meta-analysis of observational studies focusing on the factors that can predict different outcomes of ulcerative colitis was undertaken. Eligible studies were identified through an electronic search of bibliographic databases until October 2013 (Medline through PubMed, ISI Web of Knowledge and Scopus databases). The method included the definition of eligibility criteria, search strategies, study selection and characteristics, outcome measures, quantitative data synthesis and sensitivity analysis, methodological quality of studies, and statistical data analysis.

2.1 Eligibility criteria

Observational studies describing prognostic factors in UC were eligible for inclusion. The criteria for inclusion were: (1) adult patients with UC; and (2) written in English and studying associations between clinical factors and colectomy. This meta-analysis was limited to clinical factors because they are easy to apply in predictive models of outcome. Genetic, serologic, and biomarker studies were excluded because they are not universally used and are useful tools at only some centers. The only exception was C-reactive protein (CRP), to enhance the comprehensiveness of the analysis. We therefore tried to analyze predictive tools applicable at the bedside by all physicians. Studies not in English, without an available abstract, studying only genetic or serologic factors, biomarker studies (with exception of CRP), or those addressing diagnosis or quality of life were excluded. Furthermore, clinical trials were also not used since they often did not contain sufficient information to determine risk factors associated with our outcome.

2.2 Search strategy

To gather a more sensitive set of data, we defined a search query with several outcomes, looking to capture studies that, although focused on other outcomes, might provide useful information regarding colectomy as well. A literature search was therefore performed using PubMed with the following keywords and MeSH terms: '('colitis, ulcerative'[MeSH Terms] OR ('colitis'[All Fields] AND 'ulcerative'[All Fields]) OR 'ulcerative colitis'[All Fields]) AND ('Prognosis'[Mesh] OR prognostic[All Fields] OR factor[All Fields] OR predictor[All Fields]) AND ('corticoids'[All Fields] OR 'steroids'[MeSH Terms] OR 'steroids'[All Fields] OR 'colectomy'[MeSH Terms] OR 'colectomy'[All Fields] OR 'recurrence'[MeSH Terms] OR 'recurrence'[All Fields] OR 'relapse'[All Fields])'. Literature searches were also undertaken in the Scopus database and the ISI Web of Knowledge using the same search keywords: ('ulcerative colitis' AND ('prognostic' OR 'factor' OR 'predictors') AND ('corticoids' OR 'steroids' OR 'colectomy' OR 'relapse')).

2.3 Study selection and data collection process

The studies were screened and selected by two reviewers. First, all titles and abstracts were read and the inclusion and exclusion criteria were applied. Second, the reviewers read the full text of all papers considered for inclusion after abstract selection, again applying the inclusion and exclusion criteria. The following properties of each study were recorded: location and type of study, total number of patients, characteristics of included patients, definitions of outcomes, and clinical or demographic factors. Quality was assessed using a qualitative classification of the risk of bias. We used a four-item classification based on the MOOSE[5] and STROBE[6] checklists. The items were chosen based on the factors that can incorporate bias, i.e., inclusion and exclusion criteria, justification of the cohort (eligibility criteria, sources and methods of selecting participants, and methods used to describe follow-up), disease assessment (if UC was evaluated or self-reported), and outcome adjustments for potential confounders.

2.4 Predictors of UC

The predictors evaluated were: gender, disease extent, smoking habits, hospitalization at any time, use of corticoids (oral or intravenous) at any time, and CRP.

2.5 Outcome measures

The main endpoint of this study was colectomy at any time during the disease course. Whenever possible, subgroup analysis was focused on (1) colectomy due to nonresponse to treatment or within 1 year after diagnosis, and (2) colectomy during the disease course.

2.6 Quantitative data synthesis and sensitivity analysis

Statistical evidence of effects is presented as described in the original studies. We compared the groups using random effects meta-analysis weighted by the inverse of variance to estimate the odds ratio (OR) and 95% confidence interval (95% CI). Raw data were first converted to the OR using classic methods. When raw data were not available we used the hazard ratio (HR) in the analysis. All included estimates were recomputed from descriptions given in the original articles, which might result in slightly different values. All reported p-values are two-sided with a significance level of 5%. Statistical heterogeneity was assessed with the I^2 statistic; values higher than 50% indicate a substantial level of heterogeneity.[7] Review Manager v5.1 was used to calculate ORs and 95% CIs. Sensitivity analysis, to evaluate the weight of each study in the heterogeneity analysis, was performed to assess robustness of findings.

3. Results

3.1 Search and study selection

A total of 3753 articles were identified using the search strategy. After reading all titles and abstracts, 3634 articles were excluded (mostly because they did not address UC or the studied clinical factors). The reasons for exclusion are shown in Figure 1. One hundred nineteen studies were reviewed in detail and 20 articles were included.

3.2 Description of studies

Of the total of 20 studies showing clinical factors for colectomy,[8–27] 12 were conducted in Europe,[10,11,15–17,20,22–27] six in North America,[8,9,12,13,18,19] and two in Asia. Their main characteristics are summarized in Table 1. All had suitable inclusion and exclusion criteria, five did not clearly justify the cohort or disease assessment,[13,17,18,22,23] and one did not adjust the outcome for possible confounders.[28] The highest risks of bias were found for these unadjusted outcomes (Figure 2). Concerning publication bias, funnel plots were derived and did not reveal any obvious asymmetric tail other than some possible bias in disease extent, as shown later in this article (Figure 8). Also, sensitivity analysis did not show significant changes in the results for any of the outcomes.

3.3 Colectomy

Colectomy was studied as an outcome in 20 studies.[8–27] Different factors were found that could predict colectomy, namely gender, extent

Table 1. Characteristics of the included studies.

Study	Location/type of study	No. of patients	Patient characteristics	Factor	Colectomy
Ananthakrishnan (2009)[8]	North America Retrospective	246	All	Gender Disease extent Smoking Hospitalization	11%
Ananthakrishnan (2010)[9]	North America Retrospective	15 142	All	Gender Disease extent	2.4%
Desmond (2012)[10]	Europe Prospective	424	All	Gender Disease extent Hospitalization	6.8% 15.8%
Ho (2004)[11]	Europe Retrospective	167	All	Gender Disease extent Smoking Corticosteroids CRP	40%
Nguyen (2006)[12]	North America Retrospective	23 389	Age 5–80 years at UC diagnosis	Gender	10.3/1000 hospital days
Hefti (2009)[13]	North America Retrospective	561	Minimum of 7 years of UC, no colectomy, and at least one colonoscopy	Disease extent Corticosteroids	17%
Shiga (2010)[14]	Asia	296	With at least 1 year of treatment and without colectomy 1 month after treatment (no response)	Gender Disease extent CRP	14.5%
Solberg (2009)[15]	Europe	519	All	Gender Disease extent Smoking	9.8%
Triantafillidis (1998)[16]	Europe Retrospective	413	All	Gender Disease extent	16.7%
Hoie (2007)[17]	Europe Retrospective	781	All	Gender Smoking	8.7%
Samuel (2013)[18]	North America Retrospective	369	All	Gender	13.1%
Targownik (2012)[19]	North America Retrospective	3752	At least 25 years of follow-up	Gender Hospitalization	7.5%
Ferrante (2008)[20]	Europe Retrospective	81	Refractory UC; first infusion with infliximab before November 2006	Corticosteroids CRP	–
Kuriyama (2006)[21]	Asia	981	All	Gender Disease extent	9%
Molnar (2011)[22]	Europe Retrospective	183	Severe exacerbation of UC requiring parenteral corticosteroid therapy	Disease extent	25%
Ho (2006)[23]	Europe	86	All with information on 2 databases	Gender Disease extent Smoking	
Travis (1996)[24]	Europe Prospective	49	All	CRP	19%
Oussalah (2010)[25]	Europe Retrospective	191	All patients who received at least 1 infliximab infusion	CRP	18.8%
Lindgren (1998)[26]	Europe Retrospective	97	Patients with acute attacks	CRP	34%
Henriksen (2008)[27]	Europe Prospective	454	All	CRP	

of disease, smoking habits, hospitalization, and the need for corticosteroids at any time during the course of UC. The random effects model showed that female patients had a lower risk of colectomy (OR 0.78 [95% CI 0.68, 0.90]) and there was no evidence of statistical heterogeneity (I^2 = 49%) Figure 3. Regarding disease extent and colectomy risk, ten cohorts were found. The random effects model showed that patients with extensive disease had a higher risk of colectomy (OR 3.68 [95% CI 2.39, 5.69]); however, significant heterogeneity was found among them (I^2 = 67%) Figure 4. Concerning smoking habits, the random effects model showed that patients who smoked had a lower risk of colectomy (OR 0.55 [95% CI 0.33, 0.91]), with no significant heterogeneity (I^2 = 0%) Figure 5.

4.2. CLINICAL PREDICTORS OF COLECTOMY IN PATIENTS WITH ULCERATIVE COLITIS: SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

Patients hospitalized at any time had a higher risk of colectomy (OR 4.13 [95% CI 3.23, 5.27]) and there was no evidence of statistical heterogeneity (I^2 = 0%) Figure 6. An association between the use of corticosteroids and colectomy was found in four studies. Patients who took corticosteroids (oral or intravenous) at any time had a higher risk of colectomy (OR 2.10 [95% CI 1.05, 4.22]); however, significant heterogeneity was found (I^2 = 54%) Figure 7.

Subgroup analysis was performed on the outcome, addressing colectomy due to nonresponse to treatment or within 1 year after diagnosis, and colectomy during the disease course. This analysis was done only for gender, disease extent, and smoking because the number of studies did not allow any conclusion to be drawn for the remaining factors. For gender (Figure 3), disease extent (Figure 4), and smoking habits (Figure 5), no significant differences were found in those receiving surgery within the first year after diagnosis or thereafter.

In the evaluation of CRP as a predictive factor for colectomy, seven papers showed different types of risk estimation, heterogeneity in the time of CRP measurement, and different cut-offs for risk assessment, making aggregation impossible. In three studies the median or mean CRP level was not given,[14,20,25] the median was given in one work,[11] and the mean with standard deviation was given in two[24,26]; moreover, the assay for CRP measurement was not given in any study, which made it difficult to draw any relevant conclusion. In all but one study[14] there was a trend for high rates of colectomy in those with a high CRP. Ho et al.[11] provided a risk index to aid the identification of patients who did not respond to treatment (and were submitted to colectomy), with higher CRP levels in nonresponders (6.9 versus 3.9 mg/L, $p < 0.02$), although Shiga et al.[14] reported that CRP was not associated with a risk of colectomy, either at diagnosis (HR 0.93 [95% CI 0.86, 1.02]) or

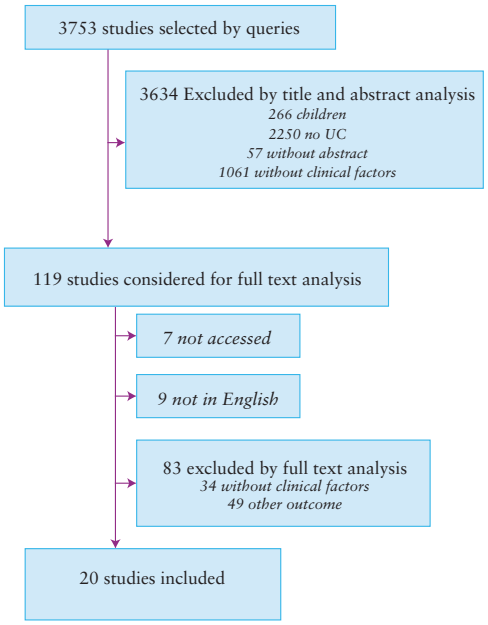

Figure 1. Study selection.

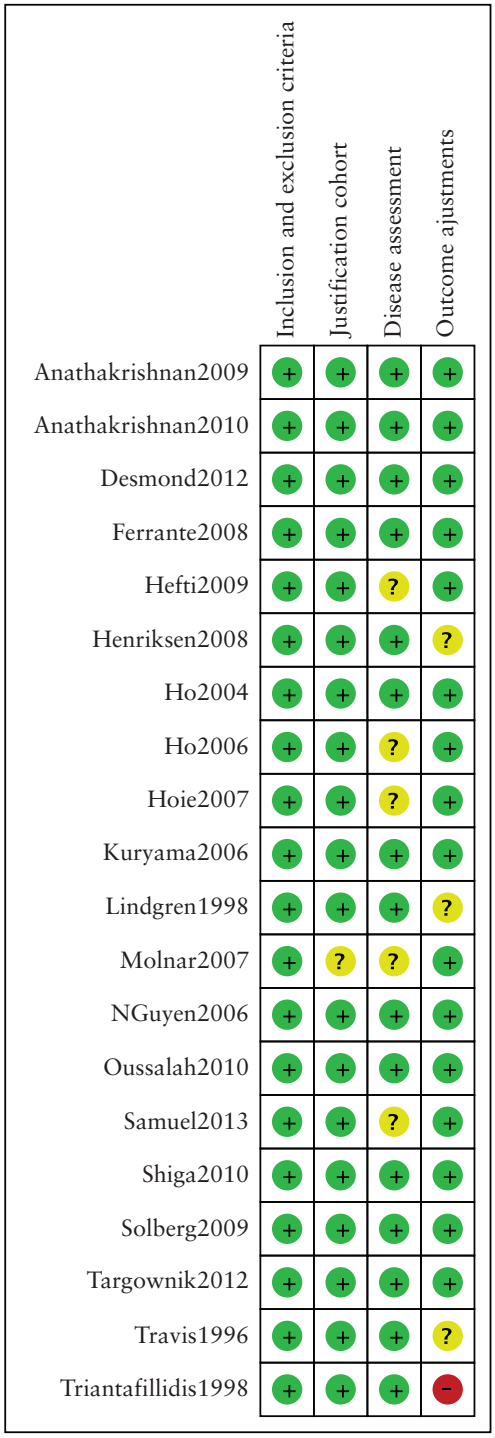

Figure 2. Summary of risk of bias.

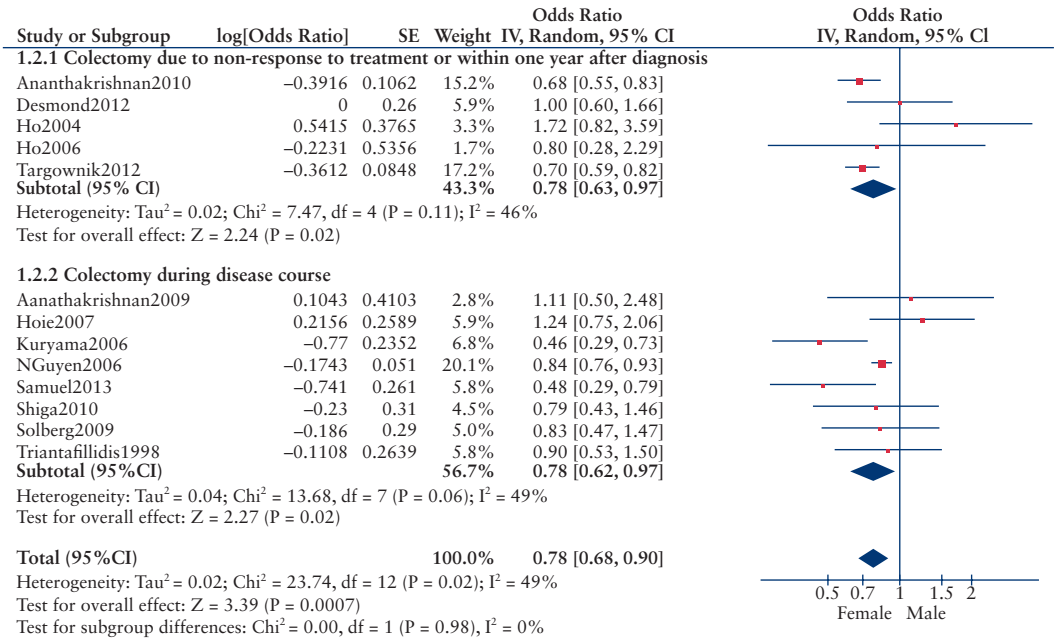

Figure 3. Gender as a predictor of colectomy.

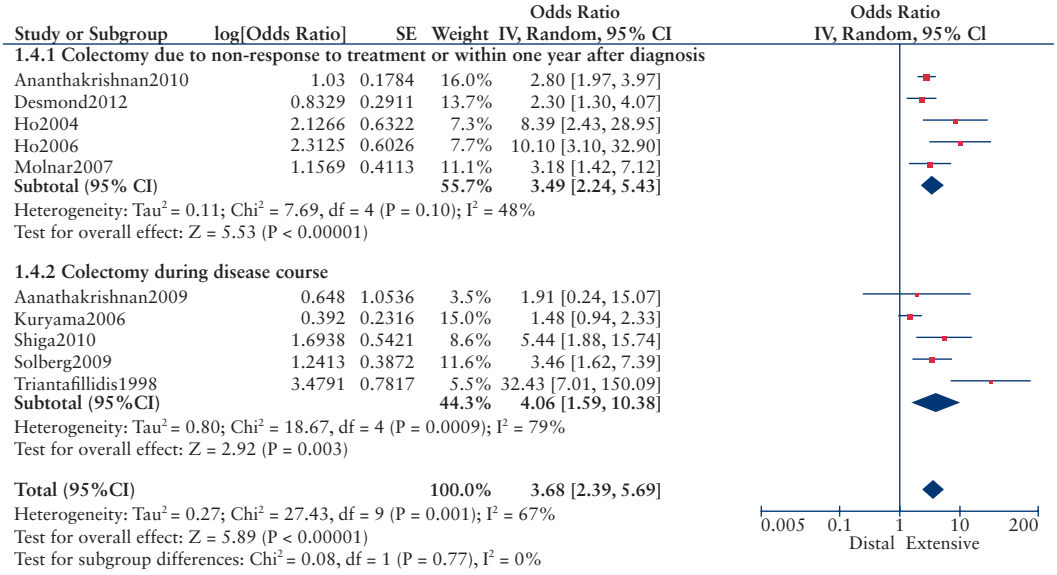

Figure 4. Disease extent as a predictor of colectomy.

4 weeks after the first induction therapy (HR 1.15 [95% 0.82, 1.62]). Patients who required colectomy[24] had higher values of CRP at admission than other patients (mean [sd] 116 [102] versus 43 [25] mg/L). Lindgren et al.[26] also identified CRP (on the third day of hospitalization) ≥25 mg/L as a predictor of colectomy, in the first 30 days of hospitalization, and colectomized patients had a higher value of CRP (on day third day after treatment) than other patients (36.3 versus 18.0 mg/L, p = 0.007). One year after diagnosis, patients with CRP ≥10 mg/L had a higher risk of colectomy in the following 4 years (OR 3.0 [95% CI 1.1, 7.8]).[27] At the time of infliximab induction, two studies showed an association between high CRP values and the risk of colectomy, one at CRP

4.2. CLINICAL PREDICTORS OF COLECTOMY IN PATIENTS WITH ULCERATIVE COLITIS: SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

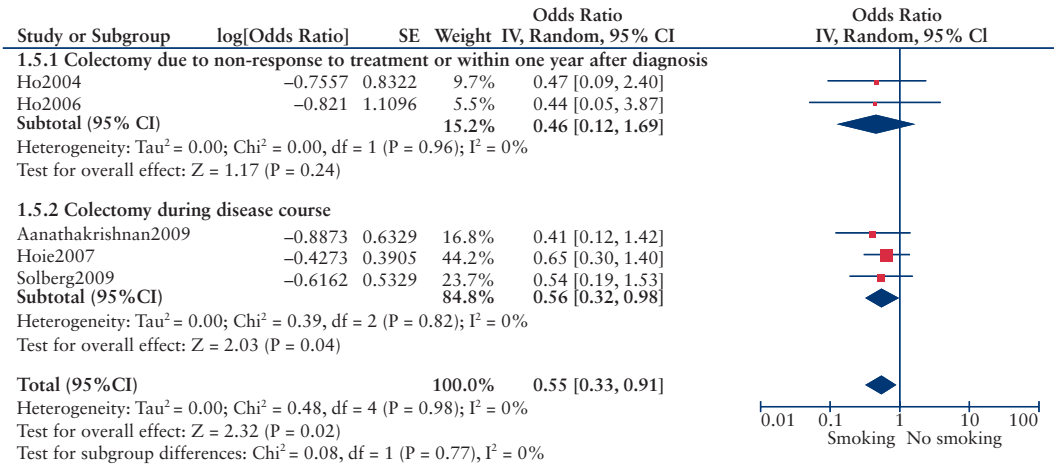

Figure 5. Smoking habits as a predictor of colectomy.

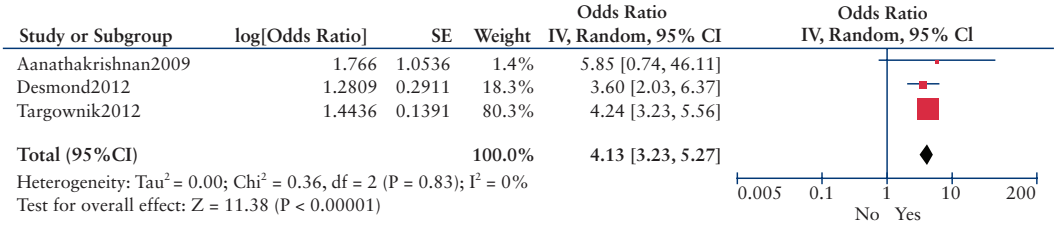

Figure 6. Hospitalization as a predictor of colectomy.

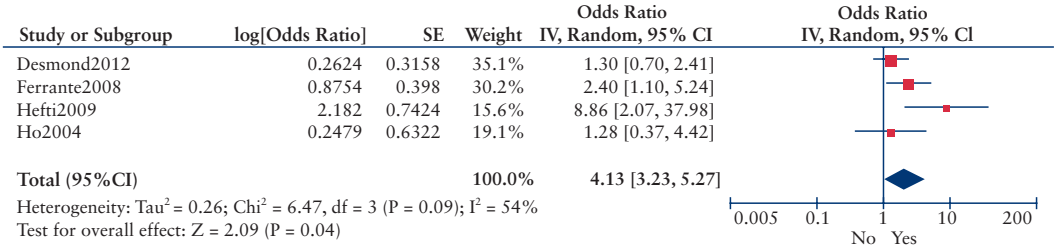

Figure 7. Use of the corticosteroids as a predictor of colectomy.

≥10 mg/L (HR 5.11 [95% CI 1.77, 14.76])[25] and the other at CRP ≥5 mg/L (HR 14.5 [95% CI 2.0, 108.6]).[20]

4. Discussion

There are several reasons for the importance of prognostic factors: (1) recently available drugs, namely anti-tumor necrosis factor have the potential to induce mucosal healing and prolonged clinical remission; (2) mucosal healing has been considered a therapeutic goal; and (3) early therapeutic interventions are followed by a better outcome.[29] The need to develop a specific clinical tool able to evaluate disabilities and identify specific factors as predictors is paramount. Therefore, the clinical risk factors analyzed in this meta-analysis should be considered when new scores or approaches are developed to assess the outcome of UC.

Here we show some of the features that could help clinicians to identify risk groups for UC. This is a step forward in the definition of predictors for UC, revealing their applicability and impact on disease prognosis, namely the risk of colectomy. Gender, disease extent, hospitalization, the need for corticosteroids, smoking habits, and CRP were associated with colectomy. Although other markers can help clinicians to predict the disease course of UC, namely genetic, serologic, and endoscopic findings, we limited this meta-analysis to demographic and clinical characteristics because of the feasibility of their assessment at diagnosis and at the bedside. Regarding CRP, the different types of risk estimation used and inadequate information about the method of measurement

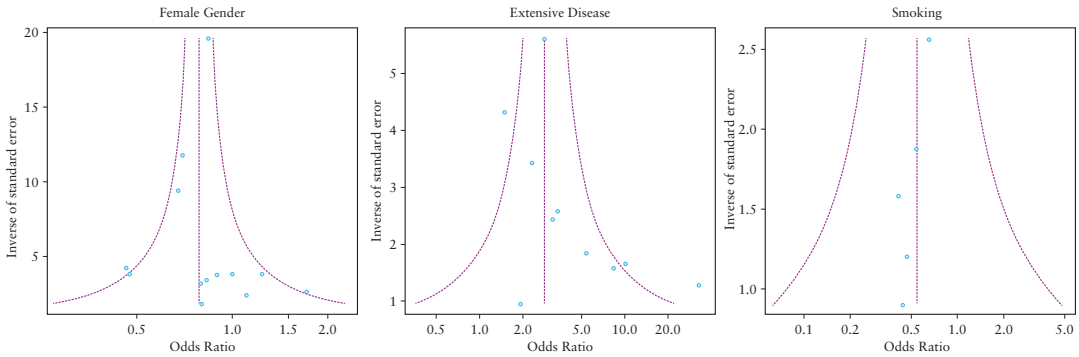

Figure 8. Funnel plots for gender, disease extent, and smoking habits as predictors of colectomy.

did not allow aggregation. However, there was a trend toward a risk of colectomy in patients with high CRP levels. The most relevant risk finding in this analysis was extensive disease and hospitalization and, in the opposite sense, smoking habits. Subgroup analysis showed that colectomy predictors were the same when the population was stratified by colectomy due to nonresponse to treatment at diagnosis or within 1 year after diagnosis, and colectomy during disease course. Gender, disease extent, and smoking remained associated factors, strengthening their value in predictive models.

We tried to evaluate more than one hospitalization per year and repeated flares requiring steroids as markers of chronic morbidity; however, there was too little information in the studies for an aggregated analysis. It was also not possible to study the roles of other clinical and demographical variables, such as age at diagnosis, because data were not available or could not be aggregated due to the different measures used. Furthermore, it was impossible to analyze several clinical trials in UC because the outcome (colectomy) was not stratified in terms of gender, disease extent, smoking habits, hospitalization, and the need for corticosteroids.

The overall quality of the included studies was good; however, we found outcome adjustment deficiencies in four of them. The main limitation found in our meta-analysis was the heterogeneity and the different approaches used. To better assess the effect of heterogeneity on our results, sensitivity analysis was performed; it showed little change in outcomes, thus supporting the robustness of our findings. However, these aspects should be taken into account in the analysis of our results and conclusions.

In summary, this review and meta-analysis showed that clinical findings such as gender, disease extent, smoking habits, hospitalization, and the need for corticosteroids are associated with the prognosis UC, namely the risk of colectomy. The use of these parameters in building predictive models for UC prognosis could enhance the clinical approach and thus improve the clinical outcome of patients with severe disease.

Author contributions

CCD was involved in the conception and design of the study and acquisition, analysis, and interpretation of data, and was responsible for drafting the manuscript; PPR was involved in the analysis and interpretation of data and drafting the manuscript; ACP was involved in interpretation of data and critically revising the manuscript; FM was involved in the conception and design of the study, interpretation of data, and drafting and revising the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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5. Classification

5. Classification

The second aim of this thesis is to identify and assess risk factors for outcomes identified in Goal 1 for Crohn's disease, using an independent cohort of patients. In this chapter we study the impact of demographical and clinical factors (such as the timing of therapeutics strategies). Early surgery or immunosuppression seem to not prevent global disabling disease, an early start of immunosuppression by itself is associated with fewer surgeries and should be considered in daily practice as a preventive strategy. Although, within surgical patients, an early surgery (within six months after diagnosis) can prevent disabling events, and the introduction of immunosuppressive medication more than one month after the initial surgery seems to increase the likelihood of needing further surgeries.

Two studies were conducted:

The impact of early surgery and immunosuppression on Crohn's disease disabling outcomes.
(*Inflammatory Bowel Diseases*, 23 (2):289-297, 2017)
Fernando Magro, Cláudia Camila Dias, Rosa Coelho, Paula Moura Santos, Samuel Fernandes, Cidalina Caetano, Ângela Rodrigues, Francisco Portela, Ana Oliveira, Paula Ministro, Eugénia Cancela, Ana Isabel Vieira, Rita Barosa, José Cotter, Pedro Carvalho, Isabelle Cremers, Daniel Trabulo, Paulo Caldeira, Artur Antunes, Isadora Rosa, Joana Moleiro, Paula Peixe, Rita Herculano, Raquel Gonçalves, Bruno Gonçalves, Helena Tavares Sousa, Luís Contente, Henrique Morna , Susana Lopes on behalf of GEDII

The timing of early therapeutics strategies has a significante impact on the Crohn's disease prognosis
(submitted, 2016)
Cláudia Camila Dias, Samuel Fernandes, Francisco Portela, Paula Ministro, Diana Martins, Paula Sousa, Paula Lago, Isadora Rosa, Luís Correia, Paula Moura Santos Fernando Magro on behalf GEDII

5.1 The impact of early surgery and immunosuppression on Crohn's disease disabling outcomes.

Inflammatory Bowel Diseases, 23 (2):289-297, 2017

Fernando Magro, Cláudia Camila Dias, Rosa Coelho, Paula Moura Santos, Samuel Fernandes, Cidalina Caetano, Ângela Rodrigues, Francisco Portela, Ana Oliveira, Paula Ministro, Eugénia Cancela, Ana Isabel Vieira, Rita Barosa, José Cotter, Pedro Carvalho, Isabelle Cremers, Daniel Trabulo, Paulo Caldeira, Artur Antunes, Isadora Rosa, Joana Moleiro, Paula Peixe, Rita Herculano, Raquel Gonçalves, Bruno Gonçalves, Helena Tavares Sousa, Luís Contente, Henrique Morna , Susana Lopes on behalf of GEDII

5.1. THE IMPACT OF EARLY SURGERY AND IMMUNOSUPPRESSION ON CROHN'S DISEASE DISABLING OUTCOMES.

ORIGINAL ARTICLE

Impact of Early Surgery and Immunosuppression on Crohn's Disease Disabling Outcomes

Fernando Magro, MD, PhD,[1,2] Cláudia C. Dias, MSc,[3,4] Rosa Coelho, MD,[5] Paula M. Santos, MD,[6] Samuel Fernandes, MD,[6] Cidalina Caetano, MD,[7] Ângela Rodrigues, MD,[7] Francisco Portela, MD,[8] Ana Oliveira, MD,[8] Paula Ministro, MD,[9] Eugénia Cancela, MD,[9] Ana I. Vieira, MD,[10] Rita Barosa, MD,[10] José Cotter, MD, PhD,[11] Pedro Carvalho, MD,[11] Isabelle Cremers, MD,[12] Daniel Trabulo, MD,[12] Paulo Caldeira, MD,[13,14] Artur Antunes, MD,[14] Isadora Rosa, MD, PhD,[15] Joana Moleiro, MD,[15] Paula Peixe, MD,[16] Rita Herculano, MD,[16] Raquel Gonçalves, MD,[17] Bruno Gonçalves, MD,[17] Helena Tavares Sousa, MD,[13,18] Luís Contente, MD,[18] Henrique Morna, MD,[19] and Susana Lopes, MD[1] on behalf of GEDII

Background and Aims: The definition of early therapeutic strategies to control Crohn's disease aggressiveness and prevent recurrence is key to improve clinical practice. This study explores the impact of early surgery and immunosuppression onset in the occurrence of disabling outcomes.

Methods: This was a multicentric and retrospective study with 754 patients with Crohn's disease, who were stratified according to the need for an early surgery (group S) or not (group I) and further divided according to the time elapsed from the beginning of the follow-up to the start of immunosuppression therapy.

Results: The rate of disabling events was similar in both groups (S: 77% versus I: 76%, $P = 0.700$). The percentage of patients who needed surgery after or during immunosuppression therapy was higher among group S, both for first surgeries after the index event (38% of groups S versus 21% of group I, $P < 0.001$) and for reoperations (38% of groups S versus 12% of group I, $P < 0.001$). The time elapsed to reoperation was shorter in group I (HR = 2.340 [1.367–4.005]), stratified for the onset of immunosuppression. Moreover, reoperation was far more common among patients who had a late start of immunosuppression (S_{36}: 50% versus S_{0-6}: 27% and S_{6-36}: 25%, $P < 0.001$) and (I_{36}: 16% versus I_{0-6}: 5% and I_{6-36}: 7%, $P < 0.001$).

Conclusions: Although neither early surgery nor immunosuppression seem to be able to prevent global disabling disease, an early start of immunosuppression by itself is associated with fewer surgeries and should be considered in daily practice as a preventive strategy.

(Inflamm Bowel Dis 2017;23:289–297)

Key Words: Crohn's disease, immunosuppression, surgery

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Crohn's disease (CD) is an idiopathic, chronic, and transmural inflammatory process that can affect the entire gastrointestinal tract, from the mouth to the anus. It is characterized by a remitting and relapsing course and can cause digestive damage and loss of function, thus being considered as a disabling condition over time.[1,2] Treatment of CD has evolved over the past few years with the appearance of anti–tumor necrosis factor α (anti-TNF α) agents and the development of new drugs, such as anti-integrin antibodies (natalizumab and vedolizumab), and a monoclonal antibody against interleukin-12 and interleukin-23 (ustekinumab).[3,4] These therapies have considerably advanced the treatment of CD and have improved the likelihood of inducing and maintaining clinical remission.[5] In addition, a significant reduction in the rate of early intestinal surgery has been described and associated with the increased use of thiopurines.[6] Nonetheless, the impact of these therapeutic changes in the paradigms that guide CD treatment remains poorly known.[1]

Surgery is nowadays considered as an option when medical therapy fails; conversely, in the past decades, surgery was an important step in CD treatment, with more than 40% of the patients being submitted to at least one disease-related abdominal surgery, most of them in the first year of the disease course.[6] More recently, Peyrin-Biroulet et al[1] described a cumulative risk of 40% to 55% to undergo surgery in the initial 10 years after diagnosis. Surgical laparoscopic approaches became increasingly common and have low complication and conversion rates, decreased morbidity, and reduced costs.[7,8] Although laparoscopy can be used safely even in those with recurrent diseases, it did not seem to decrease the risk of recurrence.[9]

The concept of "disabling disease" in inflammatory bowel disease was introduced by Beaugerie[10] in 2006 and further explored by Loly et al[11] in 2008. These authors defined disabling disease by the presence of at least one of the following criteria: 2 steroid courses required and/or steroid dependency; further hospitalization after diagnosis or complications of the disease; chronic symptoms; immunosuppressive therapy; and intestinal resection or surgical operation for perianal disease. In 2011, Yang et al[12] used a similar disabling definition but without the inclusion of chronic symptoms (diarrhea, fever, fatigue, etc.). Currently, there is no consensus regarding the definition of disabling disease; in fact, "disabling" is a dynamic concept that necessarily changes with the evolution of medical techniques and the different strategies followed to achieve disease control.

This study aimed to identify the impact of 2 different therapeutic approaches to CD—early surgery and/or immunosuppression—on disease outcomes, namely disabling events and the need for further surgeries.

METHODS

This was a nationwide, multicentric, and retrospective study. Patients with CD from 14 Portuguese inflammatory bowel disease referral centers were consecutively included. The inclusion criteria were as follows: (1) a definitive diagnosis of CD; (2) more than 3 years of follow-up; and (3) aged older than 18 years. The entire population was split into 2 groups: patients who underwent an early surgery (i.e., within the initial 6 months after diagnosis) before starting any immunosuppressive therapy (group S)—for these patients, the index event was the first surgery; and patients who started immunosuppression before any surgery (group I)—for these patients, the index event was the diagnosis. These 2 groups were further stratified by the time of the introduction of immunosuppressive medication after the index event: within the initial 6 months (very early introduction), between the 6th and the 36th month, and after the 36th month (late introduction). Being an observational study, these groups reflected the different clinical approaches motivated by the aggressiveness of the disease.

Demographic and clinical information was collected for each patient, including date of birth, date of CD diagnosis, presence of perianal disease, and smoking habits. Age at diagnosis, disease location, and phenotype were classified according to the Montreal classification.[13] The date of the first abdominal surgery and the total number of surgeries during the follow-up period were also collected, as was data concerning therapy (type and onset date). Steroid use was classified into 6 categories: never exposed to the drug, 1 steroid course per year, 2 or more steroids courses per year, 1 course every 3 years, steroid dependence, or steroid refractoriness. The definition of steroid dependence was the inability to reduce steroids below the equivalent of 10 mg/d prednisolone within 3 months of starting steroids without recurrent active disease or disease relapse within 3 months of stopping steroids. Steroid resistance was defined as the presence of active disease despite a prednisolone dose of up to 0.75 $mg \cdot kg^{-1} \cdot d^{-1}$ over a period of 4 weeks.[14] The number of hospital admissions directly related to CD and the appearance of clinical events after the index episode (fistula, abscess, stenosis, perforation, or anal disease) and the time point at which they occurred were also collected. The concept of global disabling disease was defined by the presence of one of the following criteria: more than 1 abdominal surgery or 2 hospital admissions in the follow-up period; more than 2 courses of steroids per year, steroid dependence or steroid refractoriness; need to switch the initial immunosuppressor or anti-TNF α; and the appearance of new clinical events after the index episode (fistula, abscess, stenosis, perforation, or anal disease).[15] All data were collected from a web database, and the investigators reviewed all the missing data and discrepancies. The study was monitored by the national coordinator of the Portuguese IBD group (GEDII).

Statistical Analysis

Categorical variables were described through absolute (n) and relative (%) frequencies, and continuous variables were described by their median, minimum, and maximum. Hypotheses were tested regarding the distribution of continuous variables with nonnormal distribution using the nonparametric Mann–Whitney and Kruskal–Wallis tests, depending on the nature of the hypothesis. When testing a hypothesis regarding categorical variables, a chi-square test or a Fisher's exact test was used, as appropriate.

TABLE 1. Baseline Characteristics of Patients with CD

	Total (n = 754)	Surgery (S) (n = 244)	Immune (I) (n = 510)	*P*,[a] Global
Sex, n (%)				0.905
Male	367 (48)	118 (48)	249 (48)	
Age at diagnosis, yr, n (%)				**<0.001**
A1: ≤16	67 (9)	6 (2)	61 (22)	
A2: 17–40	551 (73)	180 (74)	371 (73)	
A3: >40	136 (18)	58 (24)	78 (15)	
Location, n (%)				0.365
L1: Ileon	353 (47)	123 (51)	230 (45)	
L2: colonic	43 (6)	13 (5)	30 (6)	
L3: ileocolonic	357 (47)	107 (44)	250 (49)	
Upper tract involvement L4, n (%)	94 (12)	19 (8)	75 (15)	**0.008**
Behavior, n (%)				**<0.001**
B1: nonstricturing/nonpenetrating	239 (32)	21 (9)	218 (43)	
B2: stricturing	247 (33)	108 (44)	139 (27)	
B3: penetrating	268 (35)	115 (47)	153 (30)	
Perianal disease, n (%)	207 (27)	55 (23)	152 (30)	**0.041**
Smoking habits, n (%)				0.903
Never smoke	298 (53)	70 (53)	228 (52)	
Smoker	144 (25)	34 (26)	110 (25)	
Exsmoker	125 (22)	27 (21)	98 (23)	
Follow-up time, yr, median (min–max)	11 (3–65)	11 (3–47)	11 (3–65)	**0.954**
Therapeutics, n (%)				
Anti-TNF	194 (29)	102 (41)	120 (24)	**<0.001**
Steroids	202 (27)	87 (35)	115 (23)	**<0.001**
Disabling, n (%)				
Global	579 (77)	190 (77)	389 (76)	0.770
Surgery after index event	200 (27)	93 (38)	107 (21)	**<0.001**
Reoperation	152 (20)	93 (38)	59 (12)	**<0.001**
Total Surgeries/patients	—	1.63	0.66	

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[a]Chi-Square test.

usage of anti-TNF or steroids (Table 3). However, there were significant differences concerning age at diagnosis ($P = 0.028$), phenotype ($P = 0.016$), and smoking habits ($P = 0.021$).

Analyzing the occurrence of disabling events from a global perspective, there were no significant differences between the subgroups defined by the immunosuppression onset (Table 3). However, on analyzing the disabling criteria in an individual manner, there were statistical differences concerning the events of "surgery, hospital admissions, events," "surgery and/or hospital admission," and the occurrence of anal and stenosis events (see Table S1, Supplemental Digital Content 1, http://links.lww.com/IBD/B432). In what comes to the need for a first surgery after immunosuppression therapy, there was a borderline significant trend for an increase when the immunosuppression was initiated later ($P = 0.053$). This same trend became significant when considering reoperations only ($P = 0.001$).

After adjusting the results for all the other variables, there was no difference between the time-defined subgroups regarding occurrence of disabling disease ($I_{6–36}$: OR = 1.063 [0.562–2.011] and I_{36}: OR = 1.078 [0.617–1.866]). However, differences were found concerning disease location (L2: OR = 2.023 [1.204–3.397] and L3: OR = 4.819 [2.622–8.859], using L1 as reference) and behavior (B2: OR = 2.023 [1.204–3.397] and B3: OR = 4.819 [2.622–8.859], using B1 as reference). Concerning reoperation, patients with structuring or penetrating behavior presented a higher risk (B2: OR = 12.003 [3.975–36.242] and B3: OR = 10.436 [3.518–30.963], using B1 as reference), as did those who had a later onset of immunosuppression (I_{36}: OR = 3.090 [1.158–8.272], using $I_{0–6}$ as reference) (see Table S3, Supplemental Digital Content 3, http://links.lww.com/IBD/B432).

5.1. THE IMPACT OF EARLY SURGERY AND IMMUNOSUPPRESSION ON CROHN'S DISEASE DISABLING OUTCOMES.

Concerning the comparison of group S versus group I patients, all variables were entered in the univariate and multivariate model. On the comparison of patients stratified by the immunosuppressive therapy onset, smoking habits was not considered because of an excessive number of missing values.

The time elapsed from the index episode to the appearance of disabling disease or the need for reoperation was evaluated using survival analysis. The cumulative probabilities of event-free survival were estimated using the Kaplan–Meier method considering the group of patients using log-rank and Breslow tests.

All the reported P values were 2 sided, and $P < 0.05$ were considered statistically significant. All data were arranged, processed, and analyzed with SPSS v.23.0 (Statistical Package for Social Sciences).

RESULTS

Population

The studied cohort included 754 patients with CD who were stratified into 2 groups: group S included patients who were submitted to an early surgery (within 6 months after diagnosis), having afterward been enrolled in immunosuppressive therapy at different time points (n = 244); and group I included patients who started immunosuppressive therapy at different time points after diagnosis, but before any surgical procedure (n = 510) (Fig. 1). The demographic and clinical characteristics of the entire cohort and the 2 subgroups are shown in Table 1. Forty-eight percent of all patients were male, and 73% of them were diagnosed between 17 and 40 years of age (A2). Most patients had an ileal or an ileocolonic location of the disease, and groups S and I were similar regarding this aspect (location). Upper tract involvement was present in 12% of all patients with CD and seemed to be slightly more frequent in patients from group I (15% versus 8% in group S, $P = 0.008$). Perianal disease had a similar pattern, being present in 27% of all patients and slightly more frequent among those belonging to group I (30% versus 23% in group S, $P = 0.041$). There were also significant differences concerning the usage of anti-TNF and steroids. The distribution of phenotypes was balanced, with the exception of a noticeable smaller occurrence of B1 phenotypes among group S patients. Concerning smoking habits, there were no differences to report, as most patients in both groups have never smoked.

To further analyze these patients having into consideration the time elapsed from the index event to the start of immunosuppression therapy, both groups were stratified into 3 different categories: 0 to 6 months, 6 to 36 months, and later than 36 months (Fig. 1).

Surgery Group (Group S)

Concerning group S, there were no differences among patients with different immunosuppression starting points in what comes to sex, age at diagnosis, location, upper gastrointestinal involvement, perianal disease, smoking habits, and anti-TNF usage (Table 2). There was, however, significant differences concerning steroid intake and the Montreal classification phenotype.

The occurrence of disabling events was similar among these time-defined groups ($P = 0.372$) (Fig. 2). The absence of significant differences was maintained when analyzing the disabling criteria in an individual manner (see Table S1, Supplemental Digital Content 1, http://links.lww.com/IBD/B432). However, the need for a reoperation was far more common among patients who had a late start of immunosuppression (50% for S_{36} versus 27% and 25% for $S_{0–6}$ and $S_{6–36}$, respectively, $P < 0.001$).

After adjusting for all the other variables, there was no difference between the 3 time-defined groups in what comes to the occurrence of disabling disease ($S_{6–36}$: odds ratio [OR] = 0.776 [0.314–1.919] and S_{36}: OR = 1.559 [0.701–3.466], using S_0 as reference), but patients with perianal disease had an overall higher risk of facing disabling disease (OR = 2.814 [1.074–7.372]). Concerning reoperation, the group S_{36} had a higher risk of recurrence (OR = 2.413 [1.168–4.986]), as did patients with a stricturing phenotype (OR = 3.642 [1.029–12.897]) (see Table S2, Supplemental Digital Content 2, http://links.lww.com/IBD/B432).

Immunosuppression Group (Group I)

On stratifying patients in group I according to the time point at which they started the immunosuppression therapy, one could not find differences among the 3 groups concerning sex, disease location, perianal disease, upper tract involvement, and

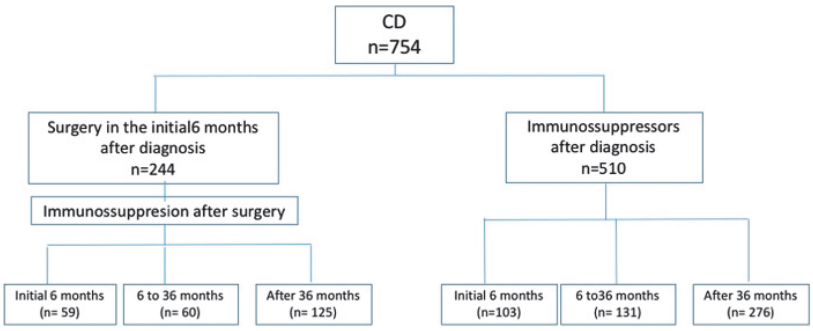

FIGURE 1. Stratification of patients in the groups.

5.1. THE IMPACT OF EARLY SURGERY AND IMMUNOSUPPRESSION ON CROHN'S DISEASE DISABLING OUTCOMES.

TABLE 2. Characteristics of Patients with CD with Surgery in the First 6 Months After Diagnosis

	S_{0-6} (n = 59)	S_{6-36} (n = 60)	S_{36} (n = 125)	P^a
Sex, n (%)				0.426
Male	27 (45)	30 (51)	69 (55)	
Age at diagnosis, yr, n (%)				0.147
A1: ≤16	3 (5)	1 (2)	2 (2)	
A2: 17–40	42 (71)	39 (65)	99 (79)	
A3: >40	14 (24)	20 (33)	24 (19)	
Location, n (%)				0.081
L1: Ileon	24 (40)	34 (58)	65 (62)	
L2: colonic	6 (10)	0 (0)	7 (6)	
L3: ileocolonic	30 (50)	25 (42)	52 (42)	
Upper tract involvement L4, n (%)	5 (9)	6 (10)	8 (7)	0.740
Behavior, n (%)				**0.023**
B1: nonstricturing/nonpenetrating	8 (13)	0 (0)	13 (11)	
B2: stricturing	22 (37)	26 (43)	60 (49)	
B3: penetrating	30 (50)	35 (57)	50 (41)	
Perianal disease, n (%)	13 (22)	13 (22)	29 (23)	0.983
Smoking habits, n (%)				0.345
Never smoke	1 (100)	21 (60)	48 (51)	
Smoker	0 (0)	5 (14)	29 (31)	
Exsmoker	0 (0)	9 (26)	18 (19)	
Follow-up time, yr, median (min–max)	6 (3–15)	7 (3–47)	16 (4–40)	<0.001
Therapeutics, n (%)				
Anti-TNF	23 (38)	28 (47)	51 (41)	0.628
Steroids	1 (2)	25 (41)	61 (49)	**<0.001**
Disabling, n (%) [95% CI]				
Global	45 (75) [69%–80%]	44 (72) [66%–78%]	101 (81) [77%–85%]	0.372
Reoperation	16 (27) [21%–33%]	15 (25) [19%–31%]	62 (50) [45%–54%]	**0.001**

Montreal classification and therapeutics.
S_{0-6}, patients with surgery in the first 6 months after diagnosis and imunossupression in the first semester after surgery; S_{6-36}, patients with surgery in the first 6 months after diagnosis and imunossupression between 6 and 36 months after surgery; S_{36}, patients with surgery in the first 6 months after diagnosis and imunossupression 36 months after surgery.
[a]Chi-square test.

Group S Versus Group I

Comparing the groups S and I in what concerns the 2 outcomes addressed in this study, one can see that there was a significant difference among the number of surgeries but no difference among the occurrence of disabling events (Table 1). In fact, global disabling disease was present in 77% of all patients enrolled and was similar between the 2 groups (77% versus 76%, $P = 0.770$). However, the need to undergo surgery after or during immunosuppression therapy was higher among group S patients, either comparing the frequency of first surgeries (38% of groups S patients versus 21% of group I patients, $P < 0.001$) or that of reoperations (38% of groups S patients versus 12% of group I patients, $P < 0.001$).

On stratifying the patients of both groups according to the time elapsed to the onset of the immunosuppressive therapy, an interesting trend emerges: although the need for a surgery increases with time in a similar fashion among patients belonging to groups I and S (Tables 2 and 3), the total number of surgeries has a dissimilar distribution (Table 1). In fact, the total number of patients undergoing surgery is higher in group S patients when compared with group I. Consequently, the overall average of surgeries is 1.63/patient and 0.66/patient in the groups S and I, respectively.

After adjusting the results for all the other variables, there were no differences between the 2 groups (S and I) in what concerns the occurrence of disabling disease (OR = 0.830 [0.465–1.481]). Nevertheless, female patients (OR = 1.636 [1.069–2.504]), patients with colonic disease (OR = 3.235 [1.019–10.269]), and patients with a B2 (OR = 2.162 [1.282–3.645]) or a B3 (OR = 4.046 [2.287–7.157]) behavior

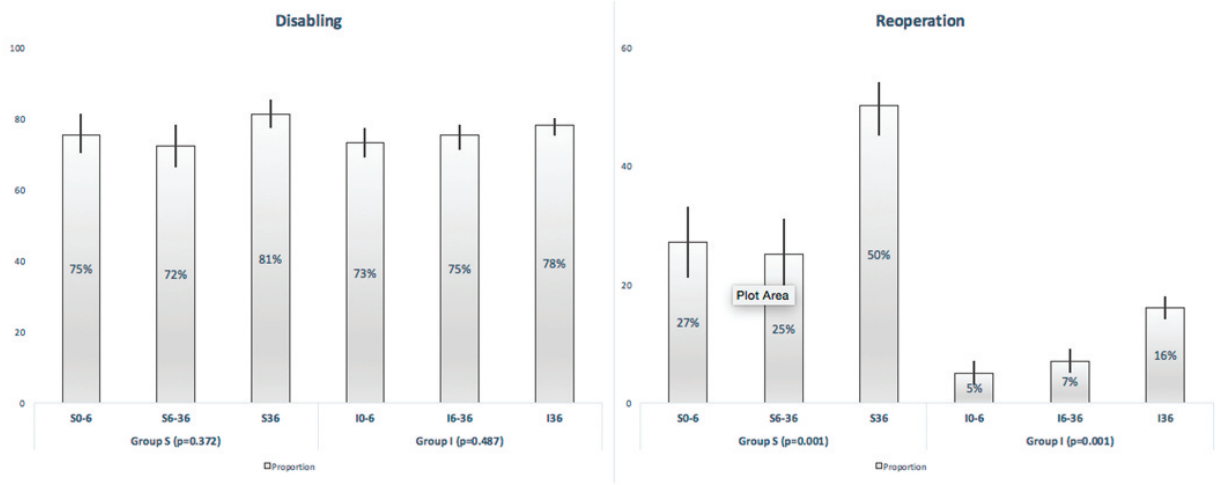

FIGURE 2. Proportion and 95% confidence interval (95% CI) of disabling disease (left) and reoperation (right) for 3 times of immunosuppression for 2 main groups (surgery and immunosuppression).

presented a higher risk of facing disabling disease. Concerning reoperation, the group I had a lower risk of recurrence (OR = 0.197 [0.117–0.330]), whereas B2 and B3 phenotype presented an increased risk (B2: OR = 8.911 [3.737–21.250] and B3: OR = 7.701 [3.281–18.072]) (see Table S4, Supplemental Digital Content 4, http://links.lww.com/IBD/B432).

The analyses of time disabling disease, adjusted to all variables, revealed that female patients and penetrating phenotype had a higher risk of disabling disease (HR = 1.127 [1.004–1.607] and HR = 1.547 [1.132–2.114], respectively), whereas no differences were found between the 2 groups S and I concerning this event (HR = 0.928 [0.706–1.220]). Regarding time to reoperation, smoker patients had a higher risk than nonsmokers (HR = 2.054 [1.169–3.610]), and patients from the group I had also a higher risk than those of group S (HR = 2.340 [1.367–4.005]) (Table 4).

DISCUSSION

This study was a national, retrospective, and observational one, which means that the therapeutic choices were performed exclusively by each physician involved according to their practice and best judgment. Patients with CD with at least 3 years of follow-up and subjected to immunosuppression therapy at some point within the 36 months after the index event (diagnosis or early surgery after diagnosis) were consecutively enrolled, and there was no intervention whatsoever from the researchers before or during patients' treatment. This study aimed at understanding whether different therapeutic options, namely early surgery and/or immunosuppression onset, had an impact on patients' outcomes concerning disabling events and further need for surgery. The rationale for the stratification based on the option for an early surgery is supported by the fact that resection is supposed to eliminate disease burden, as if there was a reset of CD in these patients. It is also important to emphasize the need to perform studies in the real world, i.e., involving heterogeneous patient populations with varying disease characteristics, as in the restrictive design of controlled trials, a number of factors influencing outcomes may remain unidentified and unrecognized.[16]

Our study shows that disabling events occur in 77% of the population and are not different between the 2 therapeutic groups analyzed. Moreover, the option for an early surgery (after diagnosis and before immunosuppressive treatment) does not decrease the likelihood of needing a second surgery. In fact, the need for reoperation in patients from group S was significantly higher than the need for a surgery (for the first time or as a reoperation) in patients belonging to group I. When we adjusted the results for all variables (sex, age at diagnosis, behavior, upper track involvement, and perianal disease), group I has a lower risk of recurrence (OR = 0.197 [0.117–0.330]). Moreover, the total number of surgeries/patient is higher in the group S (1.63) than in group I (0.66). Nevertheless, and despite the different surgical rates, both groups presented the same tendency, i.e., an increase in the need for surgeries with the increment in the time elapsed between the index event and the beginning of immunosuppressive therapy.

The importance of early therapies to prevent the recurrence of the disease in patients with CD is a cornerstone study subject. In this context, De Cruz et al[17] analyzed a cohort of 174 postoperative patients with CD divided into active care (colonoscopy at 6 months after resection and consequent medication adjustment, if needed) and standard care. Their results demonstrated that treatment according to clinical risk of recurrence with an early colonoscopy for assessment and treatment step-up was better than conventional drug therapy alone for prevention of postoperative CD recurrence.[17] Our study had a different rationale and different endpoints and was consolidated in a different background—the impact of early strategies in the prevention of disabling events.

5.1. THE IMPACT OF EARLY SURGERY AND IMMUNOSUPPRESSION ON CROHN'S DISEASE DISABLING OUTCOMES.

TABLE 3. Characteristics of Patients with CD with Imunossupression After Diagnosis

	I_{0-6} (n = 103)	I_{6-36} (n = 131)	I_{36} (n = 276)	*P*,[a] Global
Sex, n (%)				0.426
Male	27 (45)	30 (51)	69 (55)	
Age at diagnosis, yr, n (%)				**0.028**
A1: ≤16	12 (12)	16 (12)	33 (12)	
A2: 17–40	83 (80)	85 (65)	203 (74)	
A3: >40	8 (8)	30 (23)	40 (14)	
Location, n (%)				0.063
L1: Ileon	45 (44)	69 (53)	116 (42)	
L2: colonic	3 (3)	11 (8)	16 (6)	
L3: ileocolonic	55 (53)	51 (39)	144 (52)	
Upper tract involvement L4, n (%)	22 (22)	16 (12)	37 (13)	0.089
Behavior, n (%)				**0.016**
B1: nonstricturing/nonpenetrating	52 (51)	65 (50)	101 (37)	
B2: stricturing	30 (29)	29 (22)	80 (29)	
B3: penetrating	21 (20)	37 (28)	95 (34)	
Perianal disease, n (%)	30 (29)	37 (28)	85 (31)	0.866
Smoking habits				**0.021**
Never smoke	48 (68)	66 (54)	114 (47)	
Smoker	11 (15)	26 (21)	73 (30)	
Exsmoker	12 (17)	30 (25)	56 (23)	
Follow-up time, yr, median (min–max)	6 (3–36)	8 (3–25)	16 (4–65)	<**0.001**
Therapeutics				
Anti-TNF	28 (27)	31 (24)	61 (22)	0.583
Steroids	28 (27)	30 (23)	57 (21)	0.397
Disabling, n (%) [95% CI]				
Global	75 (73) [69%–77%]	98 (75) [71%–79%]	216 (78) [75%–80%]	0.487
Surgery after index event	19 (18) [14%–22%]	27 (21) [28%–25%]	80 (29) [26%–32%]	0.053
Reoperation	5 (5) [3%–7%]	9 (7) [5%–9%]	45 (16) [14%–18%]	**0.001**

Montreal classification and therapeutics.
I_{0-6}, patients with immunosuppression in the first 6 months after diagnosis; I_{6-36}, patients with immunosuppression between 6 and 36 months after diagnosis; I_{36}, patients with immunosuppression in the after 36 months after diagnosis.
[a]Chi-square test.

However, both studies are comparable in the way that both acknowledge the importance of an early intervention (either treatment adjustment after a colonoscopy or an early immunosuppression start) for the CD control and patients' management.

The concept of disabling disease in inflammatory bowel disease was introduced by Beaugerie.[10] In this work, we have chosen to use a more strict definition of this concept by applying precise criteria: abdominal surgery, hospital admissions, course of steroids/year, steroid dependence or refractoriness, need to switch immunosuppressors or anti-TNF, and the appearance of new clinical events (abscesses, fistula, anal disease, and stenosis). This change was motivated by the new tendency to prescribe immunosuppressive drugs early after diagnosis, within a window of disease opportunity, instead of using it as "the end of route."[15] The 77% rate of disabling disease reported here is similar to that of previous studies[18] and is in accordance with the known aggressiveness of CD.

At this point, it is important to clarify that the disabling events analyzed were not considered a proxy of disability: this last concept refers to a decrement in functioning and conveys the result of an interaction between health conditions and their context, including personal and environmental factors.[19] In fact, we aimed at analyzing the occurrence and timeline distribution of a series of events considered to be disabling after different therapeutic approaches, instead of obtaining an overall disability assessment.

Surgery tends to be delayed for as long as possible by patients, physicians, and even surgeons. As a consequence,

TABLE 4. Cox Regression for Time to Disabling or Time to Reoperation

	Disabling		Reoperation	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex, n (%)				
Female	1.127 (1.004–1.617)	0.046	1.453 (0.889–2.375)	0.136
Age at diagnosis, yr, n (%)				
A1: ≥16	Ref			
A2: 17–40	0.715 (0.486–1.052)	0.089	0.540 (0.217–1.347)	0.186
A3: >40	0.804 (0.503–1.285)	0.362	0.339 (0.114–1.005)	0.051
Location, n (%)				
L1: Ileon	Ref		Ref	
L2: colonic	1.197 (0.682–2.099)	0.041	0.364 (0.083–1.595)	0.180
L3: ileocolonic	0.938 (0.732–1.202)	0.744	0.624 (0.383–1.015)	0.057
Upper tract involvement L4, n (%)	1.212 (0.898–1.637)	0.209	1.293 (0.521–3.207)	0.579
Behavior, n (%)				
B1: nonstricturing/nonpenetrating	Ref		Ref	
B2: stricturing	1.302 (0.951–1.781)	0.099	2.247 (0.856–5.896)	0.100
B3: penetrating	1.547 (1.132–2.114)	0.001	2.363 (0.904–6.178)	0.079
Smoking habits				
Never smoke	Ref		Ref	
Smoker	1.073 (0.811–1.421)	0.621	1.497 (0.859–2.609)	0.155
Exsmoker	1.085 (0.808–1.458)	0.587	**2.054 (1.169–3.610)**	**0.012**
Perianal disease, n (%)	**1.325 (1.018–1.726)**	**0.037**	1.020 (0.589–1.767)	0.943
Therapeutic				
Surgery	Ref			
Immunosuppression	0.928 (0.706–1.220)	0.592	2.340 (1.367–4.005)	**0.002**

patients often come to surgery very late, with advanced or complicated diseases. Longitudinal studies suggested that patients spend a quarter (24%) of their disease course in medical remission, 41% in postoperative remission, and a further quarter (27%) with mild disease.[20,21] In the study of Aracari et. al,[22] involving 207 patients with ileocecal CD at their first resection, 83 underwent surgery at the diagnosis (early surgery), whereas 124 were submitted to surgery 54 months (min–max: 1–438) after (late surgery). Margagnoni et al[23] stated that early surgery (within 3 years after diagnosis) was associated with a longer postoperative course free from clinical recurrence when compared with late surgery, but not with reoperation, and despite higher rates of ileal and complicated disease in patients with early limited surgery, the overall need for steroids during follow-up was lower. Early surgery has been shown to represent a valid alternative to medical therapy, particularly in patients with isolated stenotic ileocecal CD. Still, Jess et al[25] reported that the rate of early surgery (in the first year after diagnosis) has fallen from 35% (1962–1987) to 12% (2003–2004). In between these time points, there was a significant change in patient management, with an increased and earlier use of immunosuppression and biological therapies. Our study supports this trend and highlights the importance of early immunosuppression, as this therapy appears to be more efficient in the prevention of surgeries than early surgery, although neither of them can prevent disabling. In a similar study by the GETAID group, early aggressive therapy with AZA within the initial 6 months after diagnosis was equally effective as conventional management in increasing time of clinical remission assessed by trimesters during 36 months.[26]

Overall, the studied groups were well balanced concerning most variables analyzed. However, one may notice that there are differences among the disease phenotype when comparing groups S and I and the different immunosuppression onset timings. In this regard, it is important to emphasize the observational nature of this study, which precludes the formation of homogeneous groups. As groups were formed retrospectively taking into consideration the clinical decisions regarding therapy, it is rational to expect different levels of disease severity as a mere reflection of the different therapeutic approaches. We believe that these differences have a reduced impact in the final analysis, as they were mostly concerned with the variation in the distribution of the less aggressive form of the disease. Moreover, it is important to highlight that there were no differences in disease location between the compared groups (either defined by the therapeutic approach or by the onset of the immunosuppressive therapy). This is particularly important because a recent article reporting the

largest genotype–phenotype association study ever performed in inflammatory bowel diseases highlighted the role of disease location as an intrinsic aspect of a patient's disease, in part genetically determined.[27] In fact, and after correcting for disease location and age at diagnosis, there was little or no genetic association with disease behavior, which tends to change dramatically over time.

The authors are aware of the possible limitations of the present work including (1) the retrospective nature of the study that, although addressed as far as possible with the adjusted regression methods, may have led to a biased underestimation of the protective effect of surgery for disabling disease; (2) the timing of the surgery in the surgical groups was determined by the clinical presentation and not by a physician's strategic decision because most of the patients were operated because of acute abdomen, abscesses, or acute symptoms; and (3) different medical and surgical strategies during the follow-up period. However, we tried to limit these drawbacks by (1) monitoring the inclusion with a data entry monitor; (2) defining the inclusion and exclusion criteria well at the beginning of the study; and (3) creating a web platform for the purpose of the study, which automatically sent missing data reports.

Overall, this study shows that neither early surgery nor early immunosuppression can prevent the occurrence of disabling events in patients with CD. However, immunosuppression as the first therapy after diagnosis is effective in preventing future surgeries, being its efficiency higher with an earlier start. However, patients undergoing an early surgery after diagnosis have an increased tendency to be reoperated, even with a concomitantly early start of immunosuppression therapy.

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5.2 The timing of early therapeutics strategies has a significant impact on the Crohn's disease prognosis

(submitted, 2016)

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

Short title: Timing of early therapy on Crohn Disease

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Abstract

Backgroud: Crohn's disease (CD) is an auto-inflammatory disease characterized by several relapses and abdominal surgery is a therapeutic option often followed by physicians for CD management. This study aims to determine the effect of the timing of the first surgical intervention on patients' prognosis.

Methods: This manuscript describes a retrospective analysis of a multicentric cohort involving 767 CD patients. Data on the disease characteristics, development and need for interventions was collected and determine the significant predictors for disabling disease and reoperation

Results: Disabling disease affected 75% of all patients and 33% needed reoperation. The Odds Ratios (OR) of being affected by disabling disease was higher when patients had colonic disease (2.615 [1.125-0.078], upper tract involvement [2.593 [1.125-6.078]] and a longer time elapsed from diagnosis to first surgery (13-36 months: 2,754[1.538-4.934] and >36 months: 2.114 [1.318-3.235]). On the other hand, the need to undergo further surgical interventions was significantly increased in patients with severe CD phenotypes (B2:3.090 [1.601-5.964] and B3: 2.440 [1.283-4.640]) , perianal disease (2.143 [1.428-3.217] and that those medicated with AZA (2.070 [1.251-3.425]) or anti-TNF (2.253 [1.522-3.334]) more than one month after the initial surgery.

Conclusions: The timing of therapeutic strategies affects the CD outcomes. Whereas an early surgery (within six months after diagnosis) can decrease the occurrence of disabling events, the introduction of immunosuppressive medication more than one month after the initial surgery seems to increase the likelihood of needing further surgeries.

Keywords: Disabling disease, reoperation, Crohn's disease

5.2. THE TIMING OF EARLY THERAPEUTICS STRATEGIES HAS A SIGNIFICANT IMPACT ON THE CROHN'S DISEASE PROGNOSIS

Introduction

Crohn's disease (CD) is a chronic auto-inflammatory disease that can affect any part of the gastrointestinal tract, and is characterized by frequent relapses (1). So far, there is no definitive treatment for CD: current therapies are meant to alleviate the symptoms and to improve patients' quality of life (2). Among these therapies, bowel surgery appears as an almost inevitable option: approximately 50% of patients undergo surgery within the first 10 years after diagnosis (3,4), whereas a total of 80% is estimated to need surgery at some time during the entire course of the disease (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 disabling disease and recurrence. Recurrence is extremely frequent and, according to the literature, affects 40% to 80% of CD patients (7,8). Information on the proportion of patients experiencing disabling disease is more variable, as the notion of "disabling" is rather dynamic and has been changing over the years with the introduction of new therapies and a better management of CD. 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. Five years after the initial study, Yang *et a*l. (11) reported a new analysis that settled the proportion of patients with disabling disease at 80%. Following the new strategies for disease control meanwhile established, this study used a slightly different definition of disabling disease.

As mentioned previously, surgery in CD patients impacts not only their quality of life, but also the likelihood of experiencing certain outcomes afterwards. For that reason, it is important to characterize the several variables associated to surgery and the specific ways in which they affect the course of the disease. This work aimed specifically at identifying the effect of the timing of the initial surgery (*i.e.*, the time elapsed from diagnosis to the first surgery) on two important CD outcomes, the occurrence of disabling events and the need for further surgeries.

Material and Methods

This was consisted in a retrospective multicentric cohort analysis of 767 CD patients being followed prospectively by six physicians attending at different hospitals. The patients' inclusion criteria were: 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 between 2014 and 2015; 4) had performed at least an X-ray computed tomography (CT) or magnetic resonance imaging (MRI) during the follow-up; and 5) the occurrence of a first abdominal surgery after the CD diagnosis.

Collected variables

All variables were prospectively collected from the Portuguese Inflammatory Bowel Disease study group (GEDII – Grupo de Estudo de Doenças

Inflamatórias Intestinais) database (gediibasedados.med.up.pt) (12). Disease location and behavior were classified according to the Montreal criteria (13). In what concerns pharmacological therapy, both the nature of the treatment – immunosuppression with azathioprine (AZA) or anti-Tumour Necrosis Factor α (anti-TNFα) – and its starting timepoint were collected.

Outcomes assessment

The primary endpoints of the study were the occurrence of disabling disease and reoperation. Disabling disease was a composite endpoint defined by the presence of at least one of the following criteria: more than one abdominal surgery or two hospital admissions in the follow-up period; steroid dependence or steroid refractoriness; need for switching the first immunosuppressive drug or anti-TNFα; and the appearance of new clinical events after the index episode (stenosis, anal disease or penetrating disease). Steroid use was classified as dependence or refractoriness. The definition of steroid dependence was the inability to reduce steroids below the equivalent of 10 mg per day, prednisolone within 3 months of starting steroids without recurrent active disease, or disease relapse within 3 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 (14). Reoperation was defined as the need for further surgeries after an initial one.

Statistical Analyses

Categorical variables were described through absolute (n) and relative (%) frequencies, while continuous variables were described as mean and standard deviation, or median, percentiles, 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 (index event) to disabling disease or reoperation was evaluated using survival analysis. This time frame was either measured between surgery and disabling disease or reoperation, or was considered to be the last known follow-up time (censored cases). The cumulative probabilities of event-free survival were estimated using the Kaplan–Meier method considering the group of patients by using LogRank and Breslow tests.

Logistic regression was applied to determine the relationship between clinical or demographical factors and the occurrence of disabling disease and reoperation. The multivariable analysis included all variables (gender, smoking habits, age at diagnosis, location disease, behavior, upper tract involvement, perianal disease and time between diagnosis and surgery). For reoperation, medical therapies (immunosuppressor and anti-TNF) were also included. These variables could not be included in the disabling analysis because the disabling definition involved medical therapies. 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 and analyzed with SPSS® v.23.0 (Statistical Package for Social Sciences).

Results

This study included a total of 767 CD patients who underwent an initial bowel surgery after diagnosis. The patients were followed for a median of 15 (IQR – 9-22) years (Table 1). Most patients were female (53%) and 53% of them have never smoked. For 72% of patients the diagnosis was made during young adulthood (17-40 years). Isolated colonic location was present in 8% of the patients, whereas 11% were reported to have upper tract involvement. Concerning behavior, the majority of patients had a severe form of the disease – 39% had stricturing and 47% had penetrating disease – whereas 24% of the patients presented perianal disease. Regarding medical therapy, 22% and 49% of patients were never treated with AZA and anti-TNF, respectively. Most patients that ended up being medicated started the treatment more than one month after surgery (43% with AZA and 36% with anti-TNF).

To study the effect of the timing of the first surgical intervention in the analyzed outcomes, patients were stratified according to the number of months elapsed from diagnosis to that initial surgery: less than 6 months, 7 to 12 months, 13 to 36 months and more than 36 months. Most patients (45%) fell into this last category, whereas for 30% the time interval was less than 6 months. For 9% and 17% of the patients the time elapsed was 7-12 and 13-36 months, respectively (Table 1).

The median (IQR) time to the introduction of AZA and anti-TNF was 65 months (13-144) and 72 months (30-143), respectively. The number of months elapsed from surgery to AZA introduction did not vary with the timing of the first surgery (p=0.095) – Fig. 1. On the other hand, the introduction of anti-TNF was done later for 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 (118 *vs.* 53 months, p<0.001) - Fig 1. Finally, the timing to the first surgery had no significant impact on the proportion of patients being medicated with AZA or anti-TNF throughout the follow up (Fig. 2), with two exceptions: the proportion of patients being treated with AZA varied with the time elapsed from the initial surgery in the intervals of 5 to 7 and 11 to 15 years after diagnosis.

Disabling Disease

During the follow up period analyzed in this study, 573 (75%) patients were considered to have 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. Regarding age at diagnosis, patients that were diagnosed as young adults (17-40 years old) were more frequently found to have disabling disease (75% *vs.* 66% without disabling, p=0.002). Moreover, the absence of upper tract involvement and perianal disease were statistically associated with the group of patients presenting no disabling disease (p=0.008 and p<0.001, respectively). Finally, patients that underwent surgery later after the diagnosis were found to be associated with disabling disease (48% *vs.* 37% without disabling), whereas those patients with an early surgery after diagnosis had a higher proportion of patients without disabling (40% *vs.*

26% with disabling), p=0.001. Accordingly, the cumulative incidence rate of disabling disease was lower in the group with early surgery (0-6 months: 65%), increasing with longer times elapsed from diagnosis to surgery. Moreover, when the patients that underwent an early surgery after diagnosis reached a status of disabling disease, they did so later than patients that had their initial surgery more than 6 months after diagnosis: the median [CI95%] was 119 [85-152] for 0-6 months, 84 [57-110] for 7-12 months, 63 [38-87] for 13-36 months, and 41 [24-57] for >36 months (p<0.001) – (Fig S1).

A multivariable logistic regression was performed to determine which factors were able to independently predict the occurrence of disabling disease in this cohort (Table 3): location, upper tract involvement and time elapsed from diagnosis to surgery were the significant variables. The odds ratio (OR) of experiencing disabling disease at some time during follow up was increased for patients with isolated colonic disease (OR=2.612, CI95% [1.125-6.078]), with upper tract involvement (OR=2.593, CI95% [1.125-6.078]), and with a longer time elapsed from diagnosis to first surgery (13-36 months: OR=2.754, CI95% [1.538-4.934]; >36 months: OR=2.114, CI95% [1.381-3.235]).

Reoperation

During the follow up period analyzed in this study, 254 (33%) of all patients needed to through more than one abdominal surgery (Table 1). The following factors were shown to be associated with the need for reoperation: age at diagnosis, disease behavior, presence of perianal disease and presence and introduction timing of pharmacological therapy (Table 4). As for the occurrence of disabling disease, most patients that required reoperation were 17 to 40 years at the time of diagnosis (79% *vs.* 69% without reoperation, p=0.001). Concerning behavior, patients with a non-structuring/non-penetrating phenotype required reoperation less often (18% *vs.* 8% with reoperation, p=0.002), as patients without perianal disease (80% vs. 66% with reoperation, p<0.001). Finally, the proportion of patients without medication was higher among those that had no reoperation (AZA: 24% *vs.* 18%, anti-TNF: 55% *vs.* 37%), whereas the proportion of patients medicated only one month after surgery was higher among those that needed reoperation (AZA: 58% *vs.* 36%, anti-TNF: 53% *vs.* 27%), p<0.001 for both cases. There was no significant difference in the cumulative incidence rates of reoperation among patients with that had their initial surgery at different timings, nor there was any difference in the time frame between surgery and reoperation: the median [95%CI] was 280 [166-393] for 0-6 months, 214 [159-268] for 7-12 months, 245 [-],for 13-36 months, and 222[142-301] for >36 months, p=0.303 (Fig S1).

The multivariable logistic regression showed that three different variables were able to independently predict the occurrence of reoperation: behavior, presence of perianal disease and the introduction and timing of the pharmacological intervention (Table 4). The ORs of requiring a reoperation at some time during the follow up period were increased for patients with more severe phenotypes (B2: OR=3.090, CI95% [1.601-5.964] and B3: OR=2.440, CI95% [1.283-4.640]), the presence of perianal disease (OR=2.143, CI95% [1.428-3.217]) and the introduction of medical therapy more than one month

after the initial surgery (AZA: OR=2.070, CI95% [1.251-3.425] and anti-TNF: OR=2.253, CI95% [1.522-3.334]).

Discussion

CD patients are likely to need at least one abdominal surgery during the course of the disease. Our hypothesis, addressed in this study, was that the time point at which patients were operated had a significant impact on the disease's prognosis, namely concerning the occurrence of disabling disease and the need for further surgeries.

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. Given the current top-down therapeutic approaches, the need to start immunosuppressive therapy and anti-TNF was not considered to be disabling disease. This was the major difference of the disabling definition used in this study compared to previous ones, and is an unavoidable consequence of a constantly increasing knowledge on the disease, followed by new therapeutic strategies for disease control and symptoms management (15–17). Disabling disease is an important outcome, as it empowers the physician with a proxy for the severity of the disease. Even using an updated and more restrictive definition of disabling disease, its estimated rate in this study was 75%, which is similar to previous ones. Likewise, disease location, the presence of perianal disease and upper tract involvement were also found to be independent predictors of disabling disease, as it has been demonstrated in other studies (18). The main novelty in this study regarding disabling disease is the realization that the time elapsed from diagnosis to an initial surgery is also an independent predictor of this outcome: in fact, patients that went through the first surgery shortly after diagnosis were less prone to suffer disabling disease during the follow-up period.

Reoperation, *i.e.*, the need to undergo more than one abdominal surgery throughout the follow-up period, is a serious and impacting complication of CD disease. Multiple risk factors – patient-related, disease-related and surgery-related – have already been identified and used to predict this outcome, but the literature is not consensual on this issue (19) . In our study, 33% of all patients needed reoperation, a similar result to that obtained in previous ones (20,21). Severe disease phenotypes, presence of perianal disease and introduction of pharmacological medication only after surgery were found to increase the reoperation risk in a significant fashion. A few studies have been published associating the introduction of medical therapeutics, namely immunosuppression, with reoperation. Immunosuppression was considered to be relevant in the CD management particularly when introduced before or after surgery as a prophylactic therapy (19). Our study was not entirely conclusive in this regard, but highlighted the increased risk for patients beginning medical therapeutics only one month after surgery.

At this point it is important to highlight that, in general, 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 when medication was introduced or on the proportion of patients being medicated throughout the follow-up (with two non-relevant exceptions). In other words, our results concerning the occurrence of disabling disease and need for reoperation were not biased by different therapeutic strategies regarding medication.

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 15 years IQR=9-15). However, a few cautionary notes should also be highlighted: this was a retrospective study, 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 behavior, presence of perianal disease and involvement of the upper gastrointestinal tract), 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 and anti-TNF more than one month 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.

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5.2. THE TIMING OF EARLY THERAPEUTICS STRATEGIES HAS A SIGNIFICANT IMPACT ON THE CROHN'S DISEASE PROGNOSIS

Table 1 - Demographical and clinical variables (n=767) of the cohort analysed in this study

	Total	
	n	(%)
Gender		
Male	358	47%
Female	409	53%
Smoking habits		
Never smoke	367	53%
Ex- smoker	155	23%
Smoker	166	24%
Age at diagnosis		
A1 - ≥16 years	85	11%
A2 - 17-40 years	555	72%
A3 - >40 years	127	17%
Location		
L1 - Ileon	365	23%
L2 – Colonic	57	8%
L3 - IleoColonic	269	39%
L4 (Upper tract involvement)		
No	647	89%
Yes	78	11%
Behavior		
B1 - Non-Stricturing/non-penetrating	105	14%
B2 - Stricturing	282	39%
B3 - Penetrating	338	47%
Perianal disease		
No	580	76%
Yes	187	24%
AZA		
No AZA	167	22%
AZA before and after surgery (<1 month)	108	14%
Aza only after surgery (>1 month)	324	43%
Aza only before surgery	151	20%
Anti TNF		
No anti TNF	366	49%
anti TNF before and after surgery (<1 month)	62	8%
anti TNF only after surgery (>1 month)	269	36%
anti TNF only before surgery	53	7%
Time between diagnosis and surgery		
0-6 months	227	30%
7-12 months	66	9%
13-36 months	127	17%
>36 months	342	45%
Disabling disease	573	75%
Reoperation	254	33%

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

	Disabling						p-value[1]
	No (n=194,25%)			Yes (n=573,75%)			
	n	(col %)	(Row %)	n	(col %)	(Row %)	
Gender							
Male	82	42%	23%	276	48%	77%	0.155
Female	112	58%	27%	297	52%	73%	
Smoking habits							
Never smoke	91	53%	25%	276	54%	75%	0.805
Ex- smoker	42	24%	27%	113	22%	72%	
Smoker	40	23%	24%	126	24%	76%	
Age at diagnosis							
A1	19	10%	22%	66	11%	78%	**0.002**
A2	127	66%	23%	428	75%	77%	
A3	48	24%	38%	79	14%	62%	
Location							
L1	103	59%	28%	262	51%	72%	0.124
L2	10	6%	18%	47	9%	82%	
L3	62	35%	23%	207	40%	77%	
L4							
No	173	95%	27%	474	88%	73%	**0.008**
Yes	10	5%	13%	68	12%	87%	
Behavior							
B1	31	17%	30%	74	14%	70%	
B2	63	34%	22%	219	40%	78%	0.288
B3	89	49%	26%	249	46%	74%	
Perianal disease							
No	169	87%	29%	411	72%	71%	**<0.001**
Yes	25	13%	13%	162	28%	87%	
Time between diagnosis and surgery							
0-6 months	79	40%	35%	148	26%	65%	**0.001**
7-12 months	19	10%	29%	47	8%	71%	
13-36 months	24	13%	19%	103	18%	81%	
>36 months	72	37%	21%	270	48%	79%	

[1]Chi-Square test

5.2. THE TIMING OF EARLY THERAPEUTICS STRATEGIES HAS A SIGNIFICANT IMPACT ON THE CROHN'S DISEASE PROGNOSIS

Table 3 – Logistic regression for disabling disease after surgery and reoperation.

	Disabling disease			Reoperation		
	OR	95%IC	P	OR	95%IC	P
Location			**0.041**			
L1	**Ref**			-	-	-
L2	**2.615**	**1.125-6.078**	**0.025**	-	-	-
L3	1.375	0.924-2.047	0.117	-	-	-
L4						
No	**Ref**			-	-	-
Yes	**2.593**	**1.125-6.078**	**0.025**	-	-	-
Behavior						**0.003**
B1	-	-	-	**Ref**		
B2	-	-	-	**3.090**	**1.601-5.964**	**0.001**
B3	-	-	-	**2.440**	**1.283-4.640**	**0.007**
Perianal disease						
No	-	-	-	**Ref**		
Yes	-	-	-	**2.143**	**1.428-3.217**	**<0.001**
Time between diagnosis and surgery			**0.001**			
0-6 months	**Ref**			-	-	-
7-13 months	1.645	0.813-3.331	0.166	-	-	-
13-36 months	**2.754**	**1.538-4.934**	**0.001**	-	-	-
>36 months	**2.114**	**1.381-3.235**	**0.001**	-	-	-
AZA[1]						**0.001**
No AZA	-	-	-	Ref		
AZA before and after surgery (<1 month)	-	-	-	1.263	0.658-2.425	0.482
AZA only after surgery (>1 month)	-	-	-	**2.070**	**1.251-3.425**	**0.005**
AZA before surgery	-	-	-	0.768	0.399-1.480	0.430
Anti TNF[1]	-	-	-			**<0.001**
No anti TNF	-	-	-	**Ref**		
Anti TNF before and after surgery (<1 month)	-	-	-	0.855	0.399-1.832	0.687
Anti TNF only after surgery (>1 month)	-	-	-	**2.253**	**1.522-3.334**	**<0.001**
Anti TNF before surgery	-	-	-	1.315	0.587-2.47	0.506
Hosmer –Lemshow		**0.355**			**0.435**	
Roc		**0.633 [0.584-0.682]**			**0.714 [0.673-0.754]**	

1 – AZA and Anti-TNF were not used in regression for disabling disease because medical therapeutics is one of the criteria of this outcome

Table 4 – Reoperation in patients with abdominal surgery after diagnosis (n=767).

	Reoperation						p-value
	No (n=513,67%)			Yes (n=254,33%)			
	n	(col %)	(Row %)	n	(col %)	(Row %)	
Gender							
Male	231	45%	65%	127	50%	35%	0.194
Female	282	55%	69%	127	50%	31%	
Smoking habits							
Never smoke	249	54%	68%	118	52%	32%	0.884
Ex- smoker	104	22%	67%	51	23%	33%	
Smoker	109	24%	66%	57	25%	34%	
Age at diagnosis							
A1	55	11%	65%	30	12%	35%	**0.001**
A2	355	69%	64%	200	79%	36%	
A3	103	20%	81%	24	9%	19%	
Location							
L1	251	55%	69%	114	49%	31%	0.333
L2	37%	8%	65%	20	9%	35%	
L3	170	37%	63%	99	42%	37%	
L4							
No	437	90%	68%	210	88%	32%	0.402
Yes	49	10%	63%	29	12%	37%	
Behavior							
B1	86	18%	82%	19	8%	18%	
B2	178	37%	63%	104	44%	37%	**0.002**
B3	222	46%	66%	116	48%	34%	
Perianal disease							
No	412	80%	71%	168	66%	29%	**<0.001**
Yes	101	20%	54%	86	34%	46%	
Time between diagnosis and surgery							
0-6 months	145	28%	64%	82	32%	36%	0.559
7-13 months	43	8%	65%	23	9%	35%	
13-36 months	90	18%	71%	37	45%	29%	
>36 months	232	46%	68%	110	44%	32%	
AZA							
No AZA	122	24%	73%	45	18%	27%	
AZA before and after surgery (<1 month)	75	15%	69%	33	13%	31%	**<0.001**
Aza only after surgery (>1 month)	181	36%	56%	143	58%	44%	
Aza only berore surgery	124	25%	82%	27	11%	18%	
Anti TNF							
No anti TNF	274	55%	75%	92	37%	25%	
Anti TNF before and after surgery (<1 month)	50	10%	81%	12	5%	19%	**<0.001**
Anti TNF only after surgery (>1 month)	138	27%	51%	131	53%	49%	
Anti TNF before surgery	40	8%	76%	13	5%	25%	

[1]Chi-Square test

5.2. THE TIMING OF EARLY THERAPEUTICS STRATEGIES HAS A SIGNIFICANT IMPACT ON THE CROHN'S DISEASE PROGNOSIS

Fig, 1. Box plots representing the time elapsed from surgery to introduction of AZA (left,p=0.095) and anti-TNF (right, p<0.001), stratified by the timing of the first surgery.

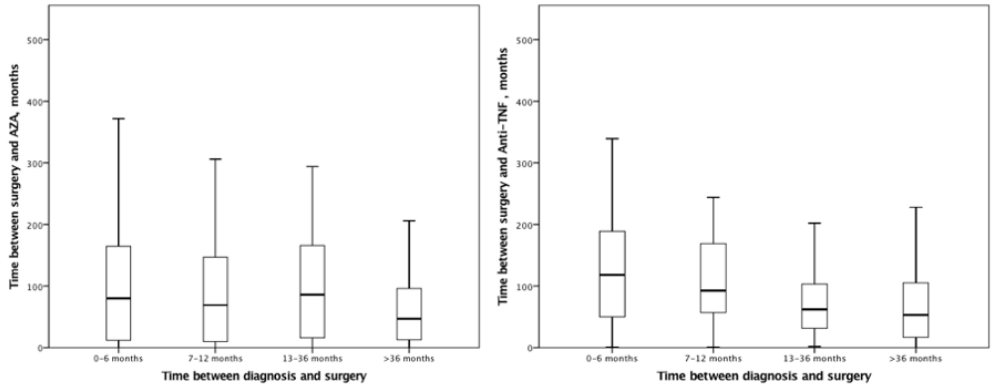
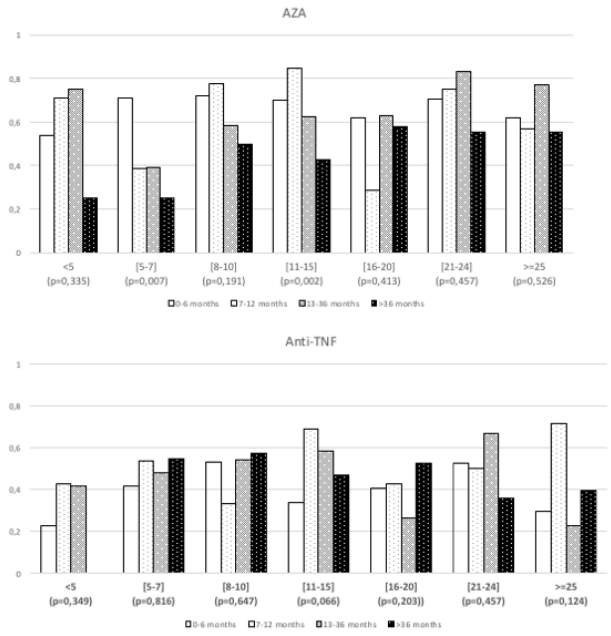
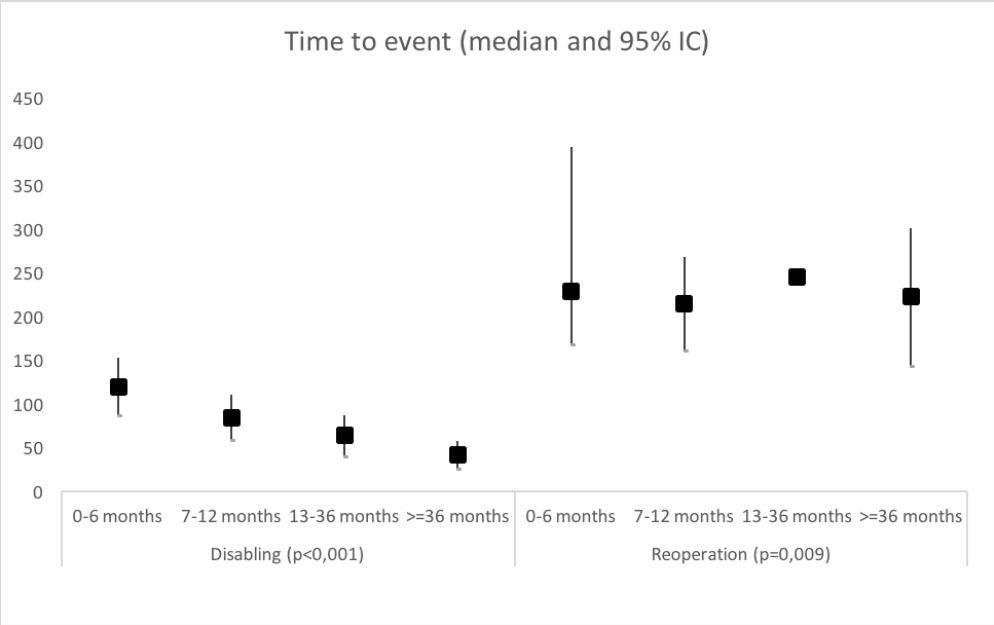


Fig. 2. Proportion of patients under AZA (up) and anti-TNF (down) therapy throughout the follow-up and stratified by the timing of the first surgery.



5.2. THE TIMING OF EARLY THERAPEUTICS STRATEGIES HAS A SIGNIFICANT IMPACT ON THE CROHN'S DISEASE PROGNOSIS

Fig. S1. Median time and 95% confidence intervals (bars) of time frame between surgery and disabling disease (right) and time frame between surgery and reoperation (left), stratified by the timing of the first surgery.



6. Prediction

6. Prediction

The third aim of this thesis is to develop and validate prognostic models for outcomes identified in Goal 1, with risk factors isolated in Goals 1 and 2. Two main paths of work have been followed for modelling predictive classifiers, one based on Bayesian networks and the other on decision trees. In the first path, two preparatory studies, presented in international forums of computer-based medical systems, were developed to a) compare Bayesian network classifiers with logistic regression (Appendix A), and b) simply assess the classification ability of the Bayesian network (Appendix B). Then, from the main study, the defined Bayesian models achieved high AUC for disabling disease and reoperation, and an online tool allows the application of the classifier at bedside (Appendix C). The risk matrices - based on age at diagnosis, perianal disease, disease aggressiveness and early therapeutic decisions - exhibited good performance for the most important prognostic criteria: high positive post-test odds for disabling disease and low negative post-test odds for reoperation. The risk matrices are also easily applicable as bedside clinical tools that can help physicians during therapeutic decisions in early disease management. In the second path, decision trees were able to predict disabling, surgery and reoperation with high AUC, and were shown to be a valid and useful approach to depict outcome risks. The defined cut-off risk levels had high odds test positivity for disabling, while excluding surgery and reoperation with low odds test negativity.

Two studies were conducted:

Development and validation of risk matrices for Crohn's disease outcomes in patients submitted to early therapeutic interventions.
Journal of Crohn's and Colitis (accepted), 2016
Cláudia Camila Dias, Pedro Pereira Rodrigues, Rosa Coelho, Paula Moura Santos, Samuel Fernandes, Cidalina Caetano, Ângela Rodrigues, Francisco Portela, Ana Oliveira, Paula Ministro, Eugnia Cancela, Ana Isabel Vieira, Rita Barosa, José Cotter, Pedro Carvalho, Isabelle Cremers, Daniel Trabulo, Paulo Caldeira, Artur Antunes, Isadora Rosa, Joana Moleiro, Paula Peixe, Rita Herculano, Raquel Gonçalves, Bruno Gonçalves, Helena Tavares Sousa, Luís Contente, Henrique Morna, Susana Lopes, and Fernando Magro on behalf of GEDII

The risk of disabling , surgery and reoperation in Crohn's disease: a decision tree-based approach to prognosis
(submitted, 2016)
Cláudia Camila Dias, Pedro Pereira Rodrigues, Samuel Fernandes, Francisco Portela, Paula Ministro, Diana Martins, Paula Sousa, Paula Lago, Isadora Rosa, Luís Correia, Paula Moura Santos, Fernando Magro on behalf GEDII

6.1 Development and validation of risk matrices for Crohn's disease outcomes in patients submitted to early therapeutic interventions.

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Original Article

Original Article

Development and Validation of Risk Matrices for Crohn's Disease Outcomes in Patients Who Underwent Early Therapeutic Interventions

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Abstract

Introduction: The establishment of prognostic models for Crohn's disease [CD] is highly desirable, as they have the potential to guide physicians in the decision-making process concerning therapeutic choices, thus improving patients' health and quality of life. Our aim was to derive models for disabling CD and reoperation based solely on clinical/demographic data.

Methods: A multicentric and retrospectively enrolled cohort of CD patients, subject to early surgery or immunosuppression, was analysed in order to build Bayesian network models and

risk matrices. The final results were validated internally and with a multicentric and prospectively enrolled cohort.

Results: The derivation cohort included a total of 489 CD patients [64% with disabling disease and 18% who needed reoperation], while the validation cohort included 129 CD patients with similar outcome proportions. The Bayesian models achieved an area under the curve of 78% for disabling disease and 86% for reoperation. Age at diagnosis, perianal disease, disease aggressiveness and early therapeutic decisions were found to be significant factors, and were used to construct user-friendly matrices depicting the probability of each outcome in patients with various combinations of these factors. The matrices exhibit good performance for the most important criteria: disabling disease positive post-test odds = 8.00 [2.72–23.44] and reoperation negative post-test odds = 0.02 [0.00–0.11].

Conclusions: Clinical and demographical risk factors for disabling CD and reoperation were determined and their impact was quantified by means of risk matrices, which are applicable as bedside clinical tools that can help physicians during therapeutic decisions in early disease management.

Key Words: Disabling disease; reoperation; Crohn's disease; risk matrices

1. Introduction

Crohn's disease [CD] is a chronic and progressive disease of unknown etiology, prone to relapses and disabling events. The clinical course is usually characterized by intermittent relapses, although half of the patients express a mild disease with low propensity to recurrent episodes. On the other hand, the more aggressive cases may require surgery.[1] As a chronic disease, neither treatment nor surgery actually heal the patients, which are usually the subject of frequent medical visits and hospitalizations, creating an aura of uncertainty surrounding their professional and social future that also affects their families.[2,3]

The new concepts on CD treatment are leaving behind the classical approach of controlling the disease symptoms—instead, studies focusing on improvement of quality of life and on the reduction of hospitalizations and surgeries are now emerging. Since the treatment schedule clearly affects the disease course, identifying good prognostic models based on genetic/serological and clinical/demographic factors have been a focus of research. The latter option is more appealing, as it can be supported by data collected during the daily clinical practice.[4,5] The identification of clinical criteria that can predict CD outcomes at an early phase of the disease is therefore crucial, as it can guide the decision-making process on the therapeutic options.

The notion of disabling disease was introduced in 2006 by Beaugerie *et al.*[6] Two years later, Lolly *et al.*[7] presented another study on this subject. Later, in 2011, Yang *et al.*[8] used a similar definition in their study. Currently, and due to the emergence of the above-mentioned new strategies for disease control, there is no consensus regarding the concept of 'disabling' in CD.

The studies seeking to identify factors that can improve the CD outcomes have conflicting conclusions, as the different cohorts yield heterogeneous results due to different methodologies and/or different criteria for patient selection and evaluation. Although the computation of prognostic models can be considered a crucial step towards CD control and management, these are, unfortunately, seldom-addressed topics in the current literature. Moreover, the intricate nature of real-world biomedical data requires the utilization of analyses in which complexity goes beyond traditional biostatistics,[9] without losing the necessary formality.[10,11]

2. Material and Methods

2.1. Derivation and validation cohorts

Data from CD patients being followed by 14 secondary and tertiary care centres was collected in a retrospective fashion [between April and December 2013]. Inclusion criteria were defined as follows: patients aged more than 18 years who had undergone surgery or immunosuppressive therapy in the initial 6 months after diagnosis, and who had at least 3 years of follow-up. All data was collected through a web database, and all missing data or discrepancies were reviewed by the investigators. The study was monitored by the national coordinator of the Portuguese IBD group [GEDII].

The independent validation cohort included patients [from five hospitals] who were enrolled in a prospective fashion. Their data were registered in a national clinical database [gediibasedados.med.up.pt] of IBD patients. Inclusion criteria were similar to those used in the derivation cohort.

Patients from both cohorts were stratified according to the early therapeutic strategies followed by their physicians: Group I patients started immunosuppression during the initial 6 months after diagnosis [index event] and prior to any surgical procedure; Group S_0 patients underwent a surgical intervention [index event] in the initial 6 months after diagnosis and had no immunosuppression therapy during the known follow-up period; and Group S_1 patients underwent a surgical intervention [index event] in the initial 6 months after diagnosis and started immunosuppression within the 6 months after surgery.

2.2. Clinical and demographic variables

Besides the basic demographic data, clinical information was collected for each patient, including the Montreal classification[12] and the follow-up data [total number of surgeries and hospitalizations; treatment, namely corticoids, immunosuppression or anti-TNF, and disease adverse events—stenosis, abscess, perforation and anal disease]. Regarding Montreal classification, patients were classified according to disease extent, behaviour and age. Steroid resistance was defined as the presence of active disease despite a prednisolone dose of up to 0.75 mg/kg per day over a period of 4 weeks.[13,14]

6.1. DEVELOPMENT AND VALIDATION OF RISK MATRICES FOR CROHN'S DISEASE OUTCOMES IN PATIENTS SUBMITTED TO EARLY THERAPEUTIC INTERVENTIONS.

2.3. Outcomes analysed

The primary outcome of this study was the occurrence of disabling disease, whereas reoperation was studied as a secondary outcome. We have defined disabling disease as the occurrence of at least one of the following events: one or more surgeries in the first 5 years after diagnosis [excluding the index surgery, if applicable]; more than one surgery during follow-up [also excluding the index surgery, if applicable]; more than two hospitalizations [excluding the index episode and hospitalization for infliximab infusion]; at least two steroid course requirements per year, steroid dependency and steroid refractoriness; need to switch immunosuppression [AZA or MTX], and anti-TNF drugs [infliximab or adalimumab]; new events such as stenosis, penetrating disease or anal disease. This definition of disabling was determined taking into account the following aspects: [1] the introduction of immunosuppression and anti-TNF per se were not interpreted as disabling disease based on the development of new therapeutic strategies; [2] due to low efficacy of 5-ASA in CD patients, many newly diagnosed patients were treated with immunosuppression and anti-TNF; [3] switching treatments was seen as disabling and [4] events after the index event were interpreted as disabling due to signs of disease progression.

2.4. Statistical analyses

Prognostic models were defined by means of Bayesian networks [BNs] built over the set of available variables.[15] Bayesian networks can be seen as an alternative to logistic regression, where statistical dependence and independence are not hidden in approximating weights, but rather explicitly represented by links in a network of variables.[11] Generally, a Bayesian network represents a joint distribution of one set of variables, specifying the assumption of independence between them, with the interdependence between variables being represented by a directed acyclic graph. Each variable is represented by a node in the graph, and is dependent on the set of variables represented by its ascendant nodes.[16] This dependence is represented by a conditional probability table that describes the probability distribution of each variable, given their ascendant variables. The Tree Augmented Naïve Bayes [TAN] classifier model, used in this study, includes two assumptions: [1] all explanatory variables are conditioned by the outcome, i.e. all will directly influence the outcome during inference; and [2] an optional additional dependence is allowed for each variable, i.e. each variable's effect might be adjusted by one additional covariable.[17] TAN classifiers were built from the derivation cohort. Model parameters were validated by comparing the AUC in the derivation cohort with those calculated from a leave-one-out and a 10 times 2-fold cross-validation [for variability assessment with independent training and testing], and by an independent comparable validation cohort.

The application of the prognostic models generated in this work can be visualized by means of [a] an online tool for direct BN inference [in beta testing phase], and [b] appropriately defined risk matrices. In order to choose which variables should be included in the risk matrices, we applied a logistic regression with all independent variables using the enter method. Variables with statistical significance [or with clinical relevance for the course of the disease, e.g. age at diagnosis[4]] were chosen as factors for the matrices. Each cell of the matrices represents the marginal posterior outcome probability estimate for that subgroup of patients. The precision of such estimates is given by a 95% credible interval, computed from a Monte Carlo simulation of one million samples from the derived joint probability model [i.e. the BN].[18] The risk values in each cell of the matrix represent the expected risk for a patient in that subgroup, while the credible interval encloses 95% of risk estimates for patients in that subgroup [i.e. only 5% of patients in that subgroup have a risk estimate outside the credible interval]. We believe that this approach is more interesting from the clinical point of view than the usual one, in which a confidence interval [CI] of the expected risk of all patients in each subgroup is computed and presented. Since patients with an early surgery [Group S] may have either engaged in immunosuppression therapy or not [S_0 *vs.* S_1], and in order to have an accurate prognosis for these patients, the posterior probability P[D|S] and the corresponding credible intervals were computed for Groups S_0 and S_1, taking into account the probability of needing immunosuppressive therapy after surgery [Table 1]. The cell risk matrices for Group S patients were calculated as follows:

$$P(D|S) = P(D|S_1) \times P(I|S) + P(D|S_0) \times P(\sim I|S).$$

To assess the discriminative ability of the risk matrices for each outcome, specific cut-off values were chosen after performing a ROC analysis of the derivation cohort. For disabling disease, and taking into account its expected prevalence and the impact of a positive prediction, a rule-in approach was applied aiming at a high positive predictive value [~80%]. For reoperation, and taking into account its expected prevalence and the impact of a negative prediction, a rule-out approach was applied aiming at a high negative predictive value [also ~80%]. The thus derived decision rules were then evaluated on both cohorts, estimating sensitivity, specificity, accuracy, the predictive values, likelihood ratios, and the post-test odds.

Logistic regression was applied with IBM SPSS v23.0, BN structures were created with WEKA software,[19] posterior probabilities were inspected using SamIam software[20]; the exact inference procedures for validation and risk matrices definition were available in R package gRain[21] using Lauritzen-Spiegelhalter algorithm,[22] while ROC curves and corresponding AUCs were computed using R package pROC.[23]

3. Results

3.1. Population characteristics and analysed outcomes

The derivation cohort analysed in this study consisted of 489 CD patients, of which 46% were male, and 79% were 40 years old or younger when diagnosed [Table 2]. Most of the patients had either an ileal or an ileocolonic location of the disease, 12% had upper tract involvement, and 26% had perianal disease. Disabling disease was observed in 64% [CI 95%: 60–68%] of the enrolled patients, while 18% [CI 95%: 15–21%] needed reoperation [i.e. more than one surgery].

Table 1. Probability of immunosuppression after surgery: P[I|S].

	Perianal disease					
	No			Yes		
	Behaviour					
	B1	B2	B3	B1	B2	B3
Age at diagnosis						
≤40	35%	80%	75%	71%	71%	83%
>40	43%	47%	67%	68%	68%	68%

I = Immunosuppression; S = Surgery.

Table 2. Characteristics of the derivation cohort enrolled in this study [*n* = 489].

	Total [*n* = 489]		Group S_0 [*n* = 80]		Group S_I [*n* = 175]		Group I [*n* = 234]		*p*-value[1]
	n	[%]	*n*	[%]	*n*	[%]	*n*	[%]	
Gender									0.914
Male	225	[46%]	36	[45%]	79	[45%]	110	[47%]	
Location									<0.001
L1. Ileal	232	[47%]	55	[69%]	95	[54%]	82	[35%]	
L2. Colonic	45	[10%]	1	[1%]	4	[2%]	40	[17%]	
L3. IleoColonic	212	[43%]	24	[30%]	76	[43%]	112	[48%]	
Upper tract involvement [L4]									<0.001
Yes	55	[12%]	2	[2%]	11	[6%]	42	[18%]	
Disease behaviour									<0.001
B1. Non-structuring/non-penetrating	158	[32%]	17	[21%]	14	[8%]	127	[54%]	
B2. Structuring	176	[36%]	35	[44%]	80	[46%]	61	[26%]	
B3. Penetrating	155	[32%]	28	[35%]	81	[46%]	46	[20%]	
Perianal disease									0.001
Yes	125	[26%]	11	[14%]	38	[22%]	76	[32%]	
Age at diagnosis									<0.001
≤40 years	388	[79%]	48	[60%]	132	[75%]	208	[89%]	
>40 years	101	[21%]	32	[40%]	43	[25%]	26	[11%]	
Follow-up time, median [IQR]	9[6–14]		13 [8–19]		13 [8–19]		6 [5–10]		<0.001
Disabling disease	314	[64%]	15	[19%]	137	[78%]	162	[69%]	<0.001
CI 95%	[60–68%]		[10–28%]		[72–84%]		[63–75%]		
Reoperation	89	[18%]	12	[15%]	70	[40%]	7	[3%]	<0.001
CI 95%	[15–21%]		[7–23%]		[33–47%]		[0.8–5%]		
Total of surgeries [including index]									–
None	132	[31%]	–		–		132	[78%]	
1	204	[48%]	68	[85%]	105	[60%]	31	[18%]	
2	52	[12%]	9	[11%]	39	[22%]	4	[2%]	
3	22	[5%]	1	[1%]	18	[10%]	3	[2%]	
4	10	[2%]	1	[1%]	9	[5%]	0	[0%]	
5	3	[1%]	1	[1%]	2	[1%]	0	[0%]	
6	1	[1%]	0	[0%]	1	[1%]	0	[0%]	
9	2	[1%]	0	[0%]	1	[1%]	1	[1%]	
Required anti-TNF	176	[37%]	0	[0%]	74	[42%]	102	[45%]	<0.001
Steroids	318	[67%]	21	[28%]	105	[63%]	192	[83%]	<0.001
1 cycle/years	57	[29%]	6	[46%]	18	[28%]	33	[28%]	0.670
≥2 cycles/year	11	[6%]	0	[0%]	5	[8%]	6	[5%]	
1 cycle for each 3 years	70	[36%]	6	[46%]	24	[37%]	40	[34%]	
Steroid dependent	46	[24%]	1	[8%]	14	[22%]	31	[27%]	
Steroid resistant	11	[6%]	0	[0%]	4	[6%]	7	[6%]	
New events									
Stenosis	74	[15%]	6	[8%]	43	[25%]	25	[11%]	<0.001
Penetrating disease	5	[1%]	2	[3%]	3	[2%]	0	[0%]	0.089
Anal disease	51	[10%]	4	[4%]	25	[14%]	23	[10%]	0.036

[1] Chi-Squared test; IQR: interquartile range; 95% CI: 95% confidence interval.

This cohort was stratified according to the early therapeutic strategies followed for each patient: Group I consisted of patients who started immunosuppression in the initial six months after diagnosis and prior to any surgical procedure, and Group S consisted of patients who underwent surgery in the initial 6 months following diagnosis. Group S was further divided into patients who started immunosuppression 6 months after the initial surgery [S_I], and patients who did not follow any immunosuppression therapy during the follow-up time considered in this study [S_0]. Eighty [16%] patients were in Group S_0, 175 [36%] in Group S_I and 234 [48%] in Group I, and significant differences were observed between these groups for all variables accounted for in this study, with the exception of gender [Table 2]. Concerning outcome, disabling disease occurred most frequently among S_I patients [78% of S_I, 69% of I and 19% of S_0, $p < 0.001$], as did the need for reoperation [40% of S_I, 3% of I and 15% of S_0, $p < 0.001$].

3.2. Bayesian prognostic models and relevant risk factors

In order to unveil the interdependent relationships between the analysed CD outcomes and the variables considered, BN-based models were built for the presence of disabling disease and the need for reoperation [Figure 1]. In both cases, patient group was associated [arc between variables] with disease behaviour, upper gastrointestinal tract location [L4], and age at diagnosis, while location was associated with perianal disease. For disabling disease, an association between perianal disease and gender was also found, whereas an association between gender and upper tract involvement was found for reoperation.

To determine which of the factors listed above were significant and should be included in risk matrices, a logistic regression was carried out using all the independent variables considered. Those that were statistically significant and those that had been shown by previous

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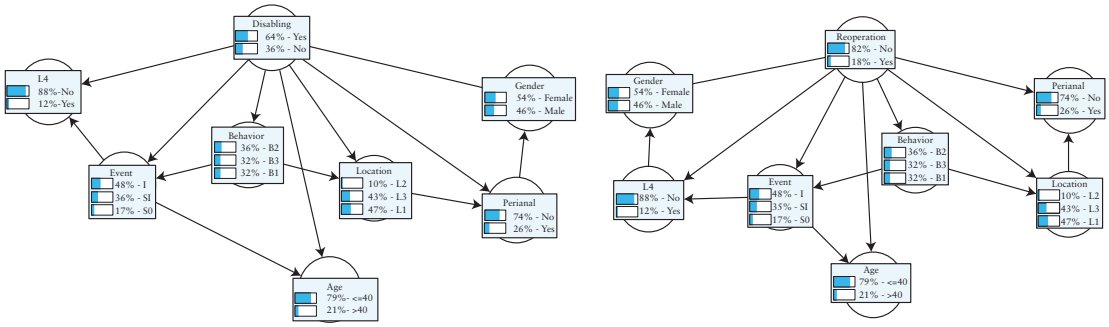

Figure 1. Bayesian network representing the relationships between each outcome [disabling disease and reoperation] and each demographic and clinical variables, and relationships between predictive factors. The bars within each variable represent the prior marginal probabilities for each variable's category. Arrows represent association between variables, but do not convey any causal relationship, the association between the outcomes and each of the remaining variables being imposed on the model.

studies to be important for the outcomes analysed[4] were selected and included in the final matrices as risk factors: for disabling disease—age at diagnosis [knowledge from literature], behaviour phenotype (B2: OR = 2.359 [1.318–4.22], B3: OR = 2.926 [1.567–5.463]), perianal disease (OR:4.340 [2.399–7.852]), and the therapeutic-defined patient group (S_1: OR=15.134 [7.483–30.607] and I: OR = 12.797 [6.128–26.723])—and for reoperation age at diagnosis (A3: OR = 0.364 [0.184–0.723]), behaviour phenotype (B2: OR = 6.443 [2.054–20.206], B3: OR = 4.815 [1.525–15.201]), perianal disease (OR: 2.189 [1.144–4.187]) and therapeutic-defined patient group (S_1: OR = 3.080 [1.500–6.325] and I: OR = 0.204 [0.073–0.571]).

3.3. Risk matrices

The risk matrices convey the risk of each outcome [disabling disease and reoperation] stratified by the relevant factors. In the particular case of this study, one of the factors considered to be relevant is the patient's group according to the initial therapeutic approaches. In this regard, it should be noticed that two of the groups are intimately linked: in fact, 52% of the patients [n = 255] were submitted to a surgical intervention during the initial six months after diagnosis, but only a fraction of those [31%] did not enter into immunosuppressive therapy afterwards, yielding Groups S_1 and S_0. Therefore, and in order to accurately depict the risk in patients who undertook surgery but have not yet started immunosuppression, one has to take into account the probability of a patient starting immunosuppression after the initial surgery, i.e. p [I|S]. Such probabilities are shown in Table 1, stratified by the other three risk factors considered to be relevant [age at diagnosis, presence of perianal disease, and disease phenotype]. The highest value [83%] was observed for patients who were 40 years old or younger at diagnosis, had perianal disease, and a penetrating disease behaviour [B3]. The lowest value [35%] was observed for patients who were 40 or younger at diagnosis, had no perianal disease, and presented the least aggressive phenotype [B1]. These results were accounted for in the construction of the final risk matrices.

3.3.1. Disabling disease

The risk for CD patients of facing disabling disease, taking into consideration the relevant factors determined previously, is stated in Table 3. Patients undergoing early surgery [Group S] had a lower probability of facing disabling disease than patients in the other two groups. For the other three risk factors considered, one could detect an increased risk when patients were 40 years old or younger at diagnosis, had perianal disease, and a penetrating disease behaviour [B3]. The highest risk was observed for patients included in Group S_1, with perianal disease, penetrating disease behaviour [B3], and older than 40 years at diagnosis: 94% [88–98%]. The lowest risk was observed for Group S patients, who had no perianal disease, non-structuring/non-penetrating disease behaviour [B1], and who were 40 or younger at diagnosis: 27% [21–36%].

3.3.2. Reoperation

The risk for CD patients of undergoing more than one surgery [reoperation] during the course of the disease, taking into consideration the relevant factors determined previously, is stated in Table 4. Patients who had an early start of immunosuppression therapy had a lower probability of reoperation than those who had an early surgery. Moreover, younger age at diagnosis and perianal disease increased the risk of reoperation, whereas a non-structuring/non-penetrating [B1] disease behaviour decreased it. The lowest probability of reoperation was observed for patients in Group I who were older than 40 years at diagnosis, had no perianal disease, and a non-structuring/non-penetrating [B1] disease behaviour: 0.4% [0.2–0.9%]. The highest probability of reoperation was observed for patients who had undergone an early surgery and later entered into an immunosuppression therapy [Group S_1], were diagnosed before or at 40, and had perianal disease and a structuring [B2] disease behaviour: 54% [26–73%].

3.4. Model validation

The Bayesian prognostic models and the resulting risk matrices were validated following two different approaches: an internal one, which consisted of two different tests [leave-one-out and ten times 2-fold cross-validation]; and an external one, following the analysis of a prospectively recruited validation cohort. ROC analyses were performed independently for the derivation cohort and for each of the validation sets of data, and the respective AUCs, along with their 95% CIs, are illustrated in Figure 2. As was desirable, the AUC values of the validation cohort nearly overlapped those of the derivation cohort, and the AUC values of the generated sets of data for the internal validation were rather similar to the later ones. Furthermore, the overall discrimination power was high for both outcomes [78% for disabling disease and 86% for reoperation, using the derivation cohort]. Based on this, the following cut-offs were

Table 3. Risk matrix showing the probability [%] of having disabling disease during the course of the disease.

		Perianal Disease						
		No			Yes			
		B1	B2	B3	B1	B2	B3	
Age at diagnosis	≤40	27% [21–36%]	60% [57–66%]	64% [62–65%]	72% [59–78%]	77% [67–87%]	85% [74–94%]	Group S
	>40	31% [17–39%]	43% [36–50%]	60% [49–62%]	66% [50–73%]	73% [58–83%]	76% [59–87%]	
	≤40	55% [43–69%]	71% [67–79%]	77% [75–80%]	82% [75–90%]	90% [83–96%]	92% [84–97%]	Group I
	>40	45% [34–60%]	62% [58–72%]	69% [67–72%]	75% [67–86%]	86% [77–94%]	88% [78–96%]	
	≤40	53% [42–66%]	71% [67–79%]	76% [74–77%]	81% [74–89%]	90% [83–96%]	91% [83–97%]	Group S_I
	>40	63% [52–75%]	78% [75–84%]	82% [81–84%]	86% [81–92%]	93% [88–98%]	94% [88–98%]	

Patient's therapeutic group: S = surgery; S_I = surgery and immunosuppression 6 months after surgery; I = immunosuppression.

Reading example: A patient 40 years old or younger at diagnosis, without perianal disease, and disease phenotype B1 had a probability of disabling disease ranging between 27% (if he or she had a surgery [Group S]) and 55% [if in the first 6 months after diagnosis he or she had immunosuppression]. But if the patient had perianal disease, the probability of disabling disease increased: 72% with a surgery in the first 6 months after diagnosis [Group S] and 82% if immunosuppression [Group I] was conducted.

Colour scheme: White = ≤10%; green = 11–19%; yellow = 20–49%; orange = 50%-74%; red = ≥75%.

Table 4. Risk matrix showing probability [%] of reoperation during the course of the disease.

		Perianal Disease						
		No			Yes			
		B1	B2	B3	B1	B2	B3	
Age at diagnosis	≤40	9% [6–13%]	42% [36–51%]	37% [29–51%]	22% [10–32%]	44% [23–50%]	48% [23–36%]	Group S
	>40	6% [3–8%]	19% [15–26%]	20% [15–31%]	11% [4–17%]	26% [9–44%]	28% [13–36%]	
	≤40	1% [0.5–2%]	9% [5–14%]	3% [2–6%]	1% [0.5–3%]	11% [3–24%]	4% [2–7%]	Group I
	>40	0.4% [0.2–0.9%]	5% [3–8%]	2% [1–3%]	0.7% [0.2–1%]	6% [2–14%]	2% [1–4%]	
	≤40	21% [14–32%]	49% [42–58%]	41% [32–56%]	30% [12–45%]	54% [26–73%]	51% [28–59%]	Group S_I
	>40	9% [6–15%]	26% [21–34%]	20% [15–32%]	14% [5–23%]	31% [11–50%]	28% [13–35%]	

Patient's therapeutic group: S = surgery; S_I = surgery and immunosuppression 6 months after surgery; I = immunosuppression.

Reading example: A patient 40 years old or younger at diagnosis, without perianal disease, and B1 phenotype had the probability of reoperation ranging between 1% (if he or she had immunosuppression in the first 6 months after diagnosis [Group I]) and 21% (if he or she had surgery in the first 6 months after diagnosis and immunosuppression thereafter [Group S_I]). But if the patient had perianal disease, the probability of reoperation increased to 30% if a surgery occurred during the first 6 months after diagnosis and the patitent had immunosuppression 6 months after surgery [Group S_I].

Colour scheme: White = ≤10%; green = 11–19%; yellow = 20–49%; orange = 50%-74%; red = ≥75%.

determined: values above 75% [for disabling disease] and above 19% [for reoperation] were considered to be positive test results, i.e. to predict the occurrence of the respective outcome.

Table 5 presents the performance of the chosen cut-offs for each outcome in the derivation and validation cohorts. The CIs for each of the performance measures computed overlapped between the two cohorts [with only two exceptions], further validating our model. Overall, the application of the cut-offs to the validation cohort resulted in 94 % [83–98%] specificity and 89% [70–97%] PPV for disabling disease, and 96% [78–100%] sensitivity and 98% [90–99%] NPV for reoperation.

3.5. Derivation vs. validation cohorts

The validation cohort consisted of 129 patients who were prospectively enrolled in this study, and whose demographic and clinical characteristics are depicted in Table 6. The derivation and validation cohorts were shown to be similar for all variables analysed, with the exception of the presence of perianal disease [26% in the derivation cohort vs. 13% in the validation cohort, $p = 0.003$] and stratification in the three different patients' groups considered [$p < 0.001$]. To exclude the hypothesis that these differences could significantly impact the validation analysis, a new set of comparisons was carried out: the performance of the determined cut-offs was computed for the validation cohort stratified according to the presence of perianal disease [see Supplementary Table S1] and the patient's group [see Supplementary Table S2]. The performance measures were similar [i.e. the 95% CIs overlap], with a few noted exceptions that occurred in performance measures that were less relevant for the corresponding outcome.

4. Discussion

Because CD is a disabling disease that has a significant negative impact on the patient's quality of life, the construction and validation of predictive models that can anticipate negative outcomes is a cornerstone for preventive therapeutics, allowing physicians to adjust the medication in a prophylactic fashion, instead of doing so as a reaction to a flare. A few attempts to analyse risk factors from a prognosis perspective have been done in the past, but they usually involved results from genetic or serologic tests,[24,25] which are both expensive and time-consuming. Our study is, to our best knowledge, the first one to build and validate risk models for CD outcomes—disabling disease and reoperation—based solely on clinical and demographic variables, which have the key advantage of

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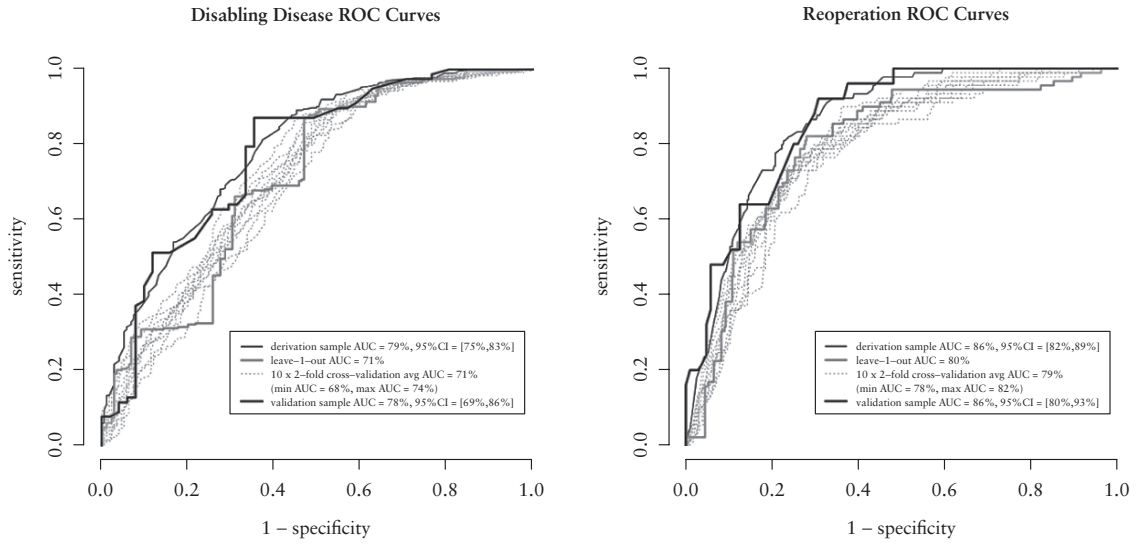

Figure 2. Receiver operating characteristic analyses and area under the curve values for the outcomes of disabling disease and reoperation in the derivation and validation cohorts, as well as for the internal validation procedures.

Table 5. Performance of risk matrix in derivation and validation cohort for disabling disease and reoperation (% [CI 95%]).

	Disabling [>75%]		Reoperation [>19%]	
	Derivation	Validation	Derivation	Validation
Sens	53% [47–58%]	31% [21–42%]	91% [85–97%]	96% [78–100%]
Spec	74% [68–80%]	94% [83–98%]	66% [61–71%]	61% [50–70%]
PPV	78% [73–83%]	89% [70–97%]	37% [31–43%]	37% [26–49%]
NPV	47% [41–53%]	47% [37–57%]	97% [95–99%]	98% [90–99%]
Accuracy	60% [55–64%]	55% [46–64%]	70% [66–74%]	67% [59–75%]
LR+	2.04 [1.55–2.68]	5.23 [1.66–16.47]	2.67 [2.29–3.09]	2.43 [1.89–3.13]
LR–	0.63 [0.57–0.72]	0.73 [0.63–0.85]	0.14 [0.07–0.27]	0.07 [0.01–0.46]
Odds post test+	3.67 [2.80–4.80]	8.00 [2.72–23.44]	0.59 [0.48–0.72]	0.58 [0.41–0.84]
Odds post test–	1.14 [1.02–1.29]	1.13 [0.91–1.38]	0.03 [0.01–0.06]	0.02 [0.00–0.11]

Sens: sensibility; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR: negative likelihood ratio.

being easily and quickly acquired. The final results were arranged into color-coded and user-friendly matrices that constitute a preliminary but useful tool that can be used by physicians in the therapeutic decision-making process.

The overall disabling rate was 64%, ranging from 19% in Group S_0 patients to 78% for Group S_I patients, values that are lower than those previously published.[6,8] However, our definition of disabling disease was stricter than that used in those studies, as variables such as 'need for immunosuppression' or 'need for anti-TNF' were not interpreted as disabling. In fact, the notion of disabling disease published by Beaugerie *et al.* has suffered a few modifications with the advent of new therapeutic strategies, namely the acceleration of step-up and the implementation of top-down treatments. We have taken these factors into account, and adjusted the concept of disabling disease to the present context. Moreover, one should keep in mind that the concept of disabling is different from that of disability. In fact, the disability index published by Peyrin-Biroulet *et al.*[26] is a multidimensional approach to disabling events, encompassing body function and structure, activities, participation, and environmental factors. As our main aim was to predict the disabling events from the clinical and demographic context of the patient, we have chosen to use the concept of disabling instead of the disability index mentioned above.

The need for more than one surgery [reoperation] occurred in 18% of all patients, a value that ranged from 40% in Group S_I to 3% in Group I. In our study, a cumulative risk of reoperation for Group S_0 ranged between 1% and 15% at 5 and 30 years of follow-up, respectively. For patients in Group S_I, the probability ranged from 0% to 41% for 5 and 30 years of follow-up, while for Group I the cumulative probability ranged between 0% and 3% for 5 and 30 years of follow-up, respectively. These values were lower than those found by Frolkis *et al.*,[27] but our cohort had a subgroup of patients who had a more aggressive treatment from diagnosis, namely immunosuppression within 6 months after diagnosis. The ability to anticipate flares and to establish preventive therapeutic strategies are invaluable steps for better disease management and a rational utilization of the available resources, especially in the case of a highly disabling and chronic disease such as CD. In this context, the Pocer study was a seminal work, establishing that retreatment according to the clinical risk of recurrence, with an early colonoscopy and treatment step-up if needed, was better than conventional drug therapy alone for the prevention of postoperative CD

Table 6. Comparison between derivation and validation cohort.

	Derivation [n = 489]		Validation [n = 129]		p-value
	n	[%]	n	[%]	
Gender					0.831
Male	225	[46%]	58	[45%]	
Location					0.817
L1. Ileal	232	[47%]	64	[50%]	
L2. Colonic	45	[9%]	13	[10%]	
L3. IleoColonic	212	[43%]	52	[40%]	
Upper tract involvement [L4]					0.714
Yes	55	[11%]	16	[12%]	
Disease behaviour					0.266
B1. Non-structuring /non-penetrating	158	[32%]	49	[38%]	
B2. Structuring	176	[36%]	37	[29%]	
B3. Penetrating	155	[32%]	43	[33%]	
Perianal disease					**0.003**
Yes	125	[26%]	17	[13%]	
Age at diagnosis					0.945
≤40 years	388	[79%]	1028	[79%]	
>40 years	101	[21%]	27	[21%]	
Disabling disease	314	[64%]	78	[61%]	0.432
Reoperation	89	[18%]	25	[19%]	0.759
Patients group					**<0.001**
S_0	80	[17%]	53	[41%]	
S_1	175	[35%]	30	[23%]	
I	234	[47%]	46	[36%]	

recurrence.[28] The rationale for our study was different, and so were the variables and the outcomes analysed, namely by including the impact of early strategies [immunosuppression and/or surgery] in the CD development. However, it is our belief that combining the results of an early endoscopic examination—after the Pocer study—with our risk matrices could greatly improve the predictive ability and increase the chances of effectively adjusting the medication in a preventive fashion.

The variables considered in the risk matrices were included after a significant result in logistic regression analysis [behaviour, patient group, and perianal disease] or because they have been previously described as predictive factors [age at diagnosis].[4,6,8] The disabling disease risk matrix showed that patients who were 40 years or less at diagnosis, have perianal disease, an aggressive disease phenotype, and who are medicated with immunosuppressors [either before any surgery or after an initial one] have a higher risk of undergoing the disabling events considered. The need for a reoperation, on the other hand, is more likely to occur in patients diagnosed at 40 or less, who have perianal disease, an aggressive disease phenotype, and who underwent an early surgery upon diagnosis. These results are in line with past research, supporting the accuracy of our matrices.[4] The embedded models' discriminative power ranges between 78% for disabling disease and 86% for reoperation. These values are higher than those presented by Siegel *et al.*,[23] a study that involved more variables, some of which of a genetic nature; therefore, our study opens new windows of opportunity for simpler yet usable models in clinical practice. The cut-offs established in our study for detecting disabling disease and reoperation [75% and 19%, respectively] were shown to have quite good performance, presenting a positive post-test odds of 8.00 [2.72–23.44] for disabling disease, and a negative post-test odds of 0.02 [0.00–0.11] for reoperation.

The BMs and risk matrices built in this study were validated using internal leave-one-out and crossed validations, as well as an independent and prospectively recruited validation cohort. The ROC curves for disabling disease and for need for reoperation were similar for the derivation and the validation cohorts. The differences between the derivation and the validation cohorts—present in the occurrence of perianal disease and formation of groups based on early therapeutic decisions—were thoroughly investigated. Whereas differences regarding the occurrence of perianal disease did not seem to impact the results, those concerning unbalanced groups of patients may convey a slight but undefined bias in the overall predictive quality of the models. In fact, in the derivation cohort, Group S_1 had a lower discriminative ability for reoperation, whereas Group I had a higher discriminative ability for the same outcome, the undefined nature of bias coming from both the groups having had a lower frequency in the validation cohort when compared with the derivation cohort.

This study had a few limitations that we acknowledge as follows: the retrospective nature of the derivation cohort, the inability to provide a close set of treatment strategies for all patients [due to lack of data], the smaller follow-up time for Group I, and the absence of data regarding patients' smoking habits. Nevertheless, we believe we have limited these drawbacks by: [i] monitoring the inclusion with a data entry monitor; [ii] precisely defining the inclusion and exclusion criteria before study start; and [iii] building a web platform for study purposes that automatically sends missing data reports. Regarding smoking status, the lack of this variable in the case report of many patients prevented its use. However, we have tested the models, including the smoking status whenever possible, and the results were similar to those we have obtained without this variable [data not shown].

As a global conclusion, we may say that our study added important knowledge to the state of the art regarding CD development—namely unveiling important risk predictive factors, including the impact of early therapeutic strategies in the disease development. Moreover, that knowledge is delivered in the form of an intuitive and user-friendly bedside predictive tool, which can be used by any

physician to quantify the likelihood of disabling events or the need for reoperation. The fact that no genetic or serologic tests results are included allows an immediate reading of this tool, allowing the early adjustment of medication and contributing to a prophylactic approach concerning CD's negative outcomes.

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Conflict of Interest

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

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Author Contributions

Dias CC was involved in the conception and design of the study, acquisition, analysis and interpretation of data, and was responsible for drafting the manuscript. Rodrigues PP was involved in the design, analysis and interpretation of data and drafting the manuscript. Coelho R was involved in interpretation of data and drafting the manuscript. Magro F was involved in the conception and design of the study, interpretation of data, and drafting and revising the manuscript. All other authors were responsible for data collection. All authors read and approved the final version of the manuscript.

Supplementary Data

Supplementary data to this article can be found at *ECCO-JCC* Online.

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6.2 The risk of disabling, surgery and reoperation in Crohn's disease: a decision tree-based approach to prognosis

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6.2. THE RISK OF DISABLING, SURGERY AND REOPERATION IN CROHN'S DISEASE: A DECISION TREE-BASED APPROACH TO PROGNOSIS

The risk of disabling, surgery and reoperation in Crohn's disease – a decision tree-based approach to prognosis

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6.2. THE RISK OF DISABLING, SURGERY AND REOPERATION IN CROHN'S DISEASE: A DECISION TREE-BASED APPROACH TO PROGNOSIS

Abstract

Introduction:
Crohn's disease (CD) is a chronic inflammatory bowel disease known to carry a high risk of disabling and many times requiring surgical interventions. The computation of prognosis models is a key step towards a better comprehension of the disease and a more efficient management of its symptoms. This article describes a decision-tree based approach that defines the CD patients' risk or undergoing disabling events, surgical interventions and reoperations, based on a particular combination of clinical and demographic variables.

Material and methods:
This multicentric study involved 1547 CD patients retrospectively enrolled and divided into two cohorts: a derivation one (80%) and a validation one (20%). Decision trees were built upon applying the CHAIRT algorithm for the selection of variables.

Results:
Three-level decision trees were built for the risk of disabling and reoperation, whereas the risk of surgery was described in a two-level one. A receiver operating characteristic (ROC) analysis was performed, and the area under the curves (AUC) revealed that the decision trees were able to predict disabling, surgery and reoperation with a probability of 72%, 80% and 69%, respectively. Risk cut-off levels were defined and shown to be useful for the outcomes assessment: risk levels above 75% for disabling had an odds test positivity of 4.06 [3.50-4.71], whereas risk levels below 34% and 19% excluded surgery and reoperation with an odds test negativity of 0.15 [0.09-0.25] and 0.50 [0.24-1.01], respectively. Globally, patients with B2 or B3 phenotype had a higher proportion of disabling disease and surgery, while patients with later introduction of pharmacological therapeutic (1 months after initial surgery) had a higher proportion of reoperation.

Conclusions:
Demographic and clinical variables can be used to accurately assess the CD patients' future risk of disabling, surgery and reoperation. The decision-tree based approach used in this study has shown to be a valid and useful approach to depict such risks.

Keywords: Disabling disease, reoperation, Crohn's disease. Risk matrices

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease for which no definitive treatment has been described. As so, clinicians approach the disease attempting to control the symptoms, avoiding disease complications and improving patients' quality of life (1). The most frequent CD complications are related to an uncontrolled inflammation of the bowel, which may cause obstruction and perforation of the small intestine or of the colon, abscess, fistulae and/or intestinal bleeding. The occurrence of these events may require a surgical intervention, which ends up being a common strategy in CD management. In fact, previous studies have reported that around 50% of all CD patients will eventually undergo bowel surgery within 10 years after the diagnosis, whereas 80% will eventually require a surgery throughout the entire disease course (1,2). Moreover, recurrence is extremely frequent, and the rate of reoperations in previous studies ranged from 40% to 80% (2,3).

As for the concept of disabling, this term was introduced by Beaugerie *et al.* in 2006 (4) and by Loly *et al.* (5) in 2008: both groups evaluated the impact of the disease using clinical and measurable criteria. These studies reported a proportion of disabling disease between 85% and 58%, respectively. Five years after the initial study on this topic, Yang *et al.* (6) presented a new report that settled the proportion of disabling at 80%. However, this last study used a slightly different definition of disabling disease. In fact, given the rapid evolution of disease control strategies, there is currently no consensus on the concept of disabling disease.

The definition of a strong and accurate prognosis model is a key step towards a better disease control and a higher quality of life in CD patients. In this context, this study aimed to unveil the differential impact of several clinical and demographic variables on the CD patients' risk of surgery, disabling and reoperation, using a decision trees-based strategy.

Material and Methods

Derivation and validation cohort

This manuscript describes a multicentric retrospective cohort study including 1547 CD patients recruited from six Portuguese inflammatory bowel disease (IBD) specialist hospitals. Patients were included if 1) had a definitive diagnosis of CD; 2) had at least three years of follow-up; 3) had at least one consultation with a physician involved in this study during 2014 or 2015; and 4) had performed at least an X-ray computed tomography (CT) or a magnetic resonance imaging (MRI) during the follow-up. A hold-out strategy was followed to enable a generalized validation of the prognostic models: the cohort was randomly split into two groups. The first one comprised 80% of patients and constituted the derivation cohort; the held-out remaining 20% of patients were considered to be the validation cohort.

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Clinical and demographic variables

All data was retrieved from GEDII (Grupo de Estudos de Doenças Inflamatórias Intestinais, the Portuguese IBD group) database (7) and included clinical and demographic variables, the dates in which the patients were submitted to bowel surgeries or started immunosuppression, and their classification regarding steroid dependence and refractoriness. The definition of steroid dependence was the inability to reduce steroids below the equivalent of 10 mg per day, prednisolone within 3 months of starting steroids without recurrent active disease, or disease relapse within 3 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 4 weeks (8). The presence and timing of immunosuppressive medication was stratified in four categories: 1) no pharmacological treatment; 2) pharmacological treatment both before and after the first surgery (started within the first month after surgery); 3) pharmacological treatment only after the surgery (starting more than 1 month after the first surgery); and 4) pharmacological treatment only before the first surgery.

Outcomes analyzed

Three different outcomes were analyzed in this study:

a) disabling disease, defined as a composite endpoint characterized by the presence of at least one of the following events: more than one abdominal surgery or two hospital admissions in the follow-up period; steroid dependence or steroid refractoriness; need for switching the first immunosuppression or anti-TNFα; and the appearance of new clinical events after the index episode (stenosis, anal disease or penetrating disease);
b) surgery, defined as the need for a surgical intervention (abdominal surgery only for CD);
c) reoperation, defined as the need for more than one surgical intervention (abdominal surgery only for CD).

Statistical analyses

The results of the statistical analysis performed during this study are summarized into decision trees, which are a graphical representation of a possible combination of variables based on specific conditions. It uses a divide-and-conquer strategy to solve a decision problem, which works by dividing a complex problem into simpler problems, recursively applying the same strategy. The different solutions of sub problems are then combined in the form of a tree to produce a solution for the original problem. Each split in the tree (a node) is produced by specifying the percentage of the outcome present in each of the categories of one independent variable (the one that has the highest impact at that level), while the final leaves convey an estimate of the outcome for the subgroup of patients that recursively traversed the tree along that path. Therefore, each path in the tree (from root to leaf) represents an exclusive decision rule associated with an estimate for the outcome. Whereas most decision trees supporting clinical decision problems are expert-based following a deductive reasoning, inductive learning the decision tree

from data, *e.g.* using recursive partitioning, is a valid method to generate a data-driven decision model (9). In order to determine the relationship between clinical/demographical factors and outcomes, decision tree classifiers were built from the derivation cohort, applying the CHAID algorithm (10), which is based upon corrected (Bonferroni post-hoc test) chi-squared significant testing. The following variables were analyzed for the outcomes disabling and surgery: gender, smoking habits, age at diagnosis, location disease, behavior, upper tract involvement (L4) and perianal disease. The presence and timing of medical therapeutics were also included when considering the outcome reoperation. The decision tree parameters were validated on the independently held-out validation cohort. The predictive quality of the leaves was evaluated on both cohorts estimating the proportion of the outcome for each of the derived rules.

To assess the discriminative ability of the trees for each outcome, specific cut-off values were chosen after analyzing the ROC curves in the derivation cohort. For disabling disease, a rule-in approach was applied aiming at a high positive predictive value (around 80%). For surgery and reoperation, a rule-out approach was applied aiming at a high negative predictive value (also around 80%). The derived trees (defining exclusive decision rules) were evaluated in both cohorts for the estimation of sensitivity, specificity, accuracy, predictive values, likelihood ratios and post-test odds.

Variables were described through absolute (n) and relative (%) frequencies. The comparison between derivation and validation cohort was made applying a Chi-Square test. All reported p-values were two-sided, for a significance level of 5%. All data were arranged, processed and analyzed with SPSS® v.24.0 (Statistical Package for Social Sciences).

Results

Population baseline characteristics and measured outcomes

The derivation cohort consisted of 1245 CD patients, the majority of them female (54%), non-smokers (53%) and diagnosed as young adults (17 to 40 years old, 69%) (Table 1). Disease location and behavior were classified according to the Montreal classifications (11): 16% had colonic disease and only 12% presented upper tract involvement. Concerning behavior, 46% had a non stricturing/non penetrating phenotype, whereas 26% had perianal disease. Disabling disease occurred in 68% of patients, 47% underwent bowel surgery, and 38% (among the latter) needed reoperation.

Disabling disease

Disabling disease occurred in 68% of the derivation cohort patients. The induced decision tree, computed from all independent variables with the exception of the presence and timing of pharmacological therapy (as this variable is itself involved in the disabling definition), resulted in a three-level model (Fig. 1). The first level was defined by the behavior phenotype, a two-way split that separated the risk for disabling of B1 (54%) apart from that of B2 and B3 phenotypes (80%). The second level consisted in the presence of perianal disease. Location and gender defined the third level for patients that

had the B1 phenotype and the absence or presence of perianal disease, respectively. The set of rules defined by this tree can be summarized by the different risk levels (32% to 90%) reported in Table 2. Globally, patients with phenotypes B2 or B3 have a higher risk of disabling disease, while for phenotype B1, gender plays an important role, with female patients having a higher risk than males.

Surgery

The outcome surgery affected 47% of the derivation cohort patients. The induced decision tree, computed using the same variables as those used for the disabling decision tree, resulted in a two-level model (Fig. 2). As for the disabling, the first level was defined by disease behavior, although in this case a three-way split separated the surgery risk of all phenotypes: 16% for B1, 68% for B2, and 75% for B3. The second level of the model included information on upper track involvement (L4) (for patients with the B2 phenotype) and gender (for patients with the B3 phenotype). The set of rules hereby defined represent different risk levels (17% to 81%), which are depicted in Table 2. Globally, patients with phenotype B3 have a higher risk of surgery than patients with B1 behavior phenotype, increased for B3 male patients compared to females.

Reoperation

The rate of reoperation was defined among those patients that underwent bowel surgery: 38% required additional surgical interventions. The induced decision tree, computed using all variables described before and including the timing and presence of pharmacological therapeutics, resulted in a three-level model of variables (Fig. 3). The first level was defined by the presence and timing of the anti-TNF introduction, separating those that started anti-TNF more than one month after surgery (53% of reoperation risk) from all the others (29% of reoperation risk). The second level included behavior for the former (stratified in B1 *vs.* B2/B3) and presence and timing of AZA introduction for the later (discriminating between patients that have either never been medicated or been medicated only before surgery from the remaining). The third level encompassed the disease location, separating L1 from L2 and L3. The defined set of rules resulted in different risk levels (13% to 58%) that are listed in Table 2. Globally, patients with later introduction of pharmacological therapeutic (1 month after initial surgery) had a worse outcome, i.e, have a higher probability of reoperation than the remaining patients.

Model Validation

The validation cohort consisted of 302 patients and was similar to the derivation cohort concerning the frequency of the analyzed variables and outcomes (Table 1). The risk of each outcome following the decision rules extracted from the trees in the derivation and validation cohorts are represented in Figure 4. The proportion of the outcomes is similar in both cohorts, and their confidence intervals are overlapping, therefore attesting the robustness of the decision rules.

Receiver operating characteristic (ROC) analysis were performed independently for the derivation and validation cohorts and the respective AUC values were similar in and had overlapping 95% CI for disabling and surgery, but not for reoperation (Fig. 5). Moreover, the AUCs were rather heterogeneous for the different outcomes: the derivation cohort presented an AUC of 72% for disabling, 80% for surgery and 69% for reoperation.
The derivation cohort ROC curves were used to establish cut-offs able to assess the likelihood of the occurrence of each outcome. Positive results were defined for risk levels above 75% concerning disabling disease, above 34% concerning surgery, and above 19% concerning reoperation. These cut-offs enabled the computation of a simplified set of rules that are listed in Table 2. The performance parameters of the chosen cut-offs considering each outcome are depicted in Table 3 for the derivation and the validation cohorts. Most of the 95% CI overlapped between both cohorts, once again validating the initial model. Overall, the application of the cut-offs to the validation cohort resulted in 81% [74%-86%] PPV for disabling disease, 87% [80%-92%] NPV for surgery, and 67% [57%-75%] for reoperation.

Discussion

Given the impact and frequency of recurrences among CD patients, the development of prognostic models is a cornerstone to guide physicians in their therapeutic choices and to improve patients' well-being. The most important characteristics of these models are their user-friendliness and readability, allowing a fast and effortless readout during patient encounters or upon the need to decide on a therapeutic approach.
This cohort presented a disabling rate of 68%, a similar value to that depicted in previous studies of different Portuguese cohorts (12,13). However, other authors have reported higher disabling rates (4–6). This difference is likely due to the fact that the disabling definition used in this study is stricter than that used in previous ones, namely by excluding the need of immunosuppression or anti-TNF as criteria. In our opinion, the introduction of pharmacological therapy not qualify as disabling, given the top-down and accelerated step-up strategies currently followed to approach CD.
Surgery, on its turn, affected 47% of the patients in the derivation cohort. This value is lower than that presented by Bernal *et al.* (2), which could be related to the fact that the cohort analyzed in that study was composed of older patients (data collected since 1955). The rapid evolution of CD therapeutics and the current strategies used to approach the disease, together with the fact that our cohort included patients that have been more recently diagnosed, explains our lower surgery rate. Moreover, a recent meta-analysis has reported a 47% risk of surgery within 10 years after diagnosis (14), thereby supporting the results described here. Reoperation, on the other hand, affected 38% of the patients who underwent a first surgery, a rate similar to that presented in a recent meta-analysis that settled the 10-years risk of reoperation at 33% (15).
The results from this study are depicted in three decision trees that represent the risk for each of the outcomes described above taking into specific

combinations of clinical and demographic variables. These decision trees were validated in an independent cohort by; a) comparing the proportion of the outcome in each derived rule; and b) comparing the diagnostic performance parameters using specific risk cut-off levels. The proportion of each outcome following the decision rules in the different cohorts was similar. Moreover, the comparison of the diagnostic performance parameters revealed that the decision trees had a good prognostic ability of concerning disabling disease and surgery: the validation cohort had a positive post-test odds for disabling disease of 4.24 [3.09-5.81], and a negative post-test odds for surgery of 0.15 [0.09-0.23]. Reoperation, on the other hand, appeared to a harder outcome to predict, presenting a less favorable performance among the validation cohort patients. This might indicate that other factors – besides those that have been considered – need to be included in the model. Nevertheless, the negative post-test odds of the validation cohort were 0.5 [0.24-1.01], and therefore this model might still be useful to detect patients with a lower risk of reoperation.

The variables used in the decision tree were chosen by applying the CHAID algorithm, which is similar to the chi-square with Bonferroni correction post hoc test. The final selection of variables was the same as that used in previous studies that employed different selection methods, therefore attesting the robustness of the computed decision trees (2,4–6,16–18). The decision tree analysis has a some advantages over others that are more widely used *(e.g.* logistic regression). An undeniable strength of this method is its graphical representation, which allows a quick and intuitive reading. On the other hand, decision trees are rather flexible in the way that they do not assume any data distribution. Another advantage is the attribute selection, which restricts the variables in the model to those that are non-redundant. The interpretability of the trees is also one their strong points – complex decisions can be approximated by simple or local decisions. Finally, decision trees allow an easy comparison of patients' subgroups, as decision rules can be created directly from the tree.

Globally, patients with B2 or B3 phenotype had a higher proportion of disabling disease and surgery, while patients with later introduction of pharmacological therapeutic (1 months after initial surgery) had a higher proportion of reoperation. Although retrospectively run, with retrospectively defined outcomes, this study presents an analysis of a large multicentric cohort formaly validated by the application of the derived results in a validation cohort.

In conclusion, we have shown that variables such as disease behavior, upper gastrointestinal involvement, gender, perianal disease, location and medical therapeutics affect the risk of disabling disease, surgery and reoperation in CD patients. Moreover, these variables impact the aforementioned outcomes at different levels, having different weights in sub-groups of patients with different variables' combinations. Our results are represented in three graphical and user-friendly bedside tools that can be used by the physicians to assess the risk of disabling, surgery and reoperation in CD patients, therefore supporting the decision making process regarding therapeutic strategies. A disabling risk above 75% allows the prediction of disabling events with a PPV of 81% and an odds post-test

positivity of 4.24, whereas a surgery risk inferior to 34% allows the exclusion of future surgeries with a NPV of 87% and an odds post-test negativity of 0.15. The reoperation was the hardest outcome to predict, although a risk below 19% could be useful for excluding future events (NPV: 87 and odds post-test negativity: 0.5).

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Table 1- Baseline characteristics and comparison between the derivation and the validation cohorts.

	Derivation (n=1245)		Validation (n=302)		p-value
Gender					0,409
Male	577	(46%)	132	(44%)	
Age at diagnosis					0,682
A1 - <=16 years	138	(11%)	37	(12%)	
A2- 17-40 years	865	(69%)	212	(70%)	
A3- >40 years	242	(19%)	53	(18%)	
Location					0,246
L1 - Ileon	542	(44%)	120	(40%)	
L2 – Colonic	200	(16%)	44	(15%)	
L3 - IleoColonic	503	(40%)	138	(46%)	
Upper tract involvement (L4)	152	(12%)	27	(9%)	0,111
Behaviour					0,431
B1 - Non-Stricturing/non-penetrating	572	(46%)	146	(48%)	
B2 - Stricturing	308	(25%)	64	(21%)	
B3 - Penetrating	365	(29%)	92	(30%)	
Perianal disease	327	(26%)	80	(26%)	0,937
AZA					0,403
No AZA	794	(64%)	199	(66%)	
AZA before and after surgery (<1 month)	79	(6%)	16	(5%)	
Aza only after surgery (>1 month)	270	(22%)	70	(23%)	
Aza before surgery	102	(8%)	17	(6%)	
Anti TNF					0,835
No anti TNF	943	(76%)	234	(77%)	
anti TNF before and after surgery (<1 month)	44	(4%)	9	(3%)	
anti TNF only after surgery (>1 month)	224	(18%)	53	(18%)	
anti TNF before surgery	34	(3%)	6	(2%)	
Disabling disease	849	(68%)	206	(68%)	0,995
Surgery	579	(47%)	135	(45%)	0,573
Reoperation	220	(38%)	45	(33%)	0,313

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Table 2- Decision rules and proportion and confidence intervals of outcomes observed

Disabling Disease		
	Proportion of outcome	For cut-off of 75%
B1 & No Perianal & L1	31.5% [24.4%-38.6%]	46.8% [42.0%-51.6%]
B1 & No Perianal & L2/L3	56.7% [50.6%-62.8%]	
B1 & Perianal & Male	66.7% [55.8%-77.6%]	66.7% [55.8%-77.6%]
B1 & Perianal & Female	82.7% [74.5%-90.9%]	82.7% [74.5%-90.9%]
B2/B3 & No Perianal	76.4% [72.7%-80.1%]	79.9% [76.8%-82.8%]
B2/B3 & Perianal	90.2% [87.8%-94.6%]	
Surgery		
	Proportion of outcome	For cut-off of >34%
B1	16.6% [13.5%-19.7%]	16.6% [13.5%-19.7%]
B2 & No L4	72.0% [66.4%-77.6%]	68.2% [62.3%-73.1%]
B2 & L4	51.7% [38.44%-64.6%]	
B3 & Male	81.2% [75.3%-87.1%]	75.1% [70.4%-79.2%]
B3 & Female	69.7% [63.3%-76.2%]	
Reoperation		
	Proportion of outcome	For cut-off of > 19%
TNF after surgery (> 1 month) & B2/B3	57.9% [50.9%-64.9%]	52.7 % [46.2%-59.1%]
TNF after surgery (> 1 month) & B1	23.5% [9.3%-37.8%]	
TNF (without, before or before and after surgery) & AZA (without or only before surgery) & L1	13.3% [6.6-%-20.0%]	13.3% [6.6%-20.0%]
TNF (without, before or before and after surgery) & AZA (without or only before surgery) & L2/L3	28.9% [18.7%-39.1%]	28.9% [18.7%-39.1%]
TNF (without, before and before or after surgery) & (AZA after or before and after surgery)	37.0% [30.3%-44.3%]	37.0% [18.7%-39.1%]

Logical operators: & (AND) ; White - <=10%; green – 11-19%; Yellow – 20%-49%; Orange – 50%-74% and red>=75%

Table 3 – Performance of risk matrix in derivation and validation cohort for disabling disease and reoperation (% [CI 95%])

	Disabling >75%		Surgery >34%		Reoperation >19%	
	Derivation	Validation	Derivation	Validation	Derivation	Validation
Sens	71	67	**84**	**86**	**94**	**87**
	[68-74]	[61-74]	**[80-86]**	**[78-91]**	**[89-97]**	**[73-94]**
Spec	**62**	**65**	72	76	24	13
	[57-74]	**[55-75]**	[68-75]	[69-82]	[19-28]	[7-23]
PPV	**80**	**81**	72	74	43	33
	[77-83]	**[74-86]**	[68-75]	[66-81]	[39-48]	[8-21]
NPV	50	48	**83**	**87**	**87**	**67**
	[45-55]	[40-58]	**[80-86]**	**[80-92]**	**[78-92]**	**[57-75]**
Accuracy						
LR+	1.89	1.97	2.94	3.59	1.23	1
	[1.66-2.16]	[1.47-2.65]	[2.60-3.34]	[2.71-4.74]	[1.15-1.32]	[0,67-1,15]
LR-	0.46	0.49	0.23	0.19	0.25	1,00
	[0.41-0.51]	[0.40-0.60]	[0.19-0.28]	[0.12-0.28]	[0.14-0.43]	[0,41-2,43]
Odds post test+	**4.06**	**4.24**	2.56	2.90	0.75	0,5
	[3.50-4.71]	**[3.09-5.81]**	[2.25-2.92]	[2.18-3.85]	[0.66-0.86]	[0,37-0,67]
Odds post test-	0.99	1.05	**0.20**	**0.15**	**0.15**	**0,5**
	[0.90-1.08]	[0.87-1.26]	**[0.16-0.24]**	**[0.09-0.23]**	**[0.09-0.25]**	**[0,24-1,01]**

Sens: Sensibility; Spec: Specifity; PPV: Positive Predictive value; NPV: Negative Predictive value; LR+: Positive Likelihood ratio: LR-: Negative Likelihood ratio

6.2. THE RISK OF DISABLING, SURGERY AND REOPERATION IN CROHN'S DISEASE: A DECISION TREE-BASED APPROACH TO PROGNOSIS

Figure 1- Decision tree for disabling disease

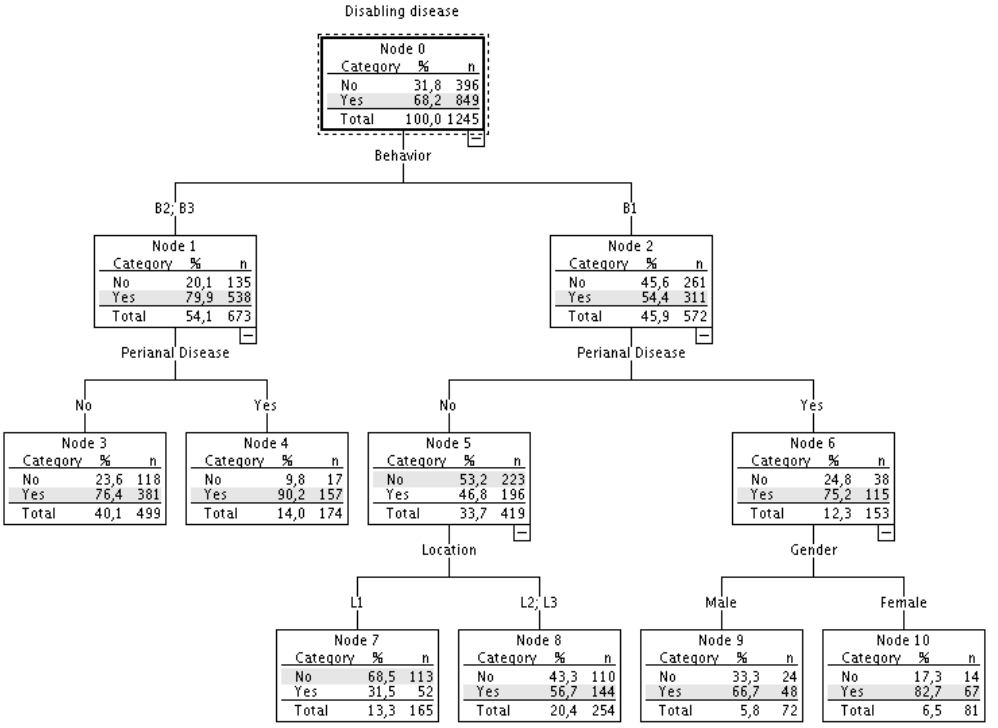


Figure 2- Decision tree for surgery

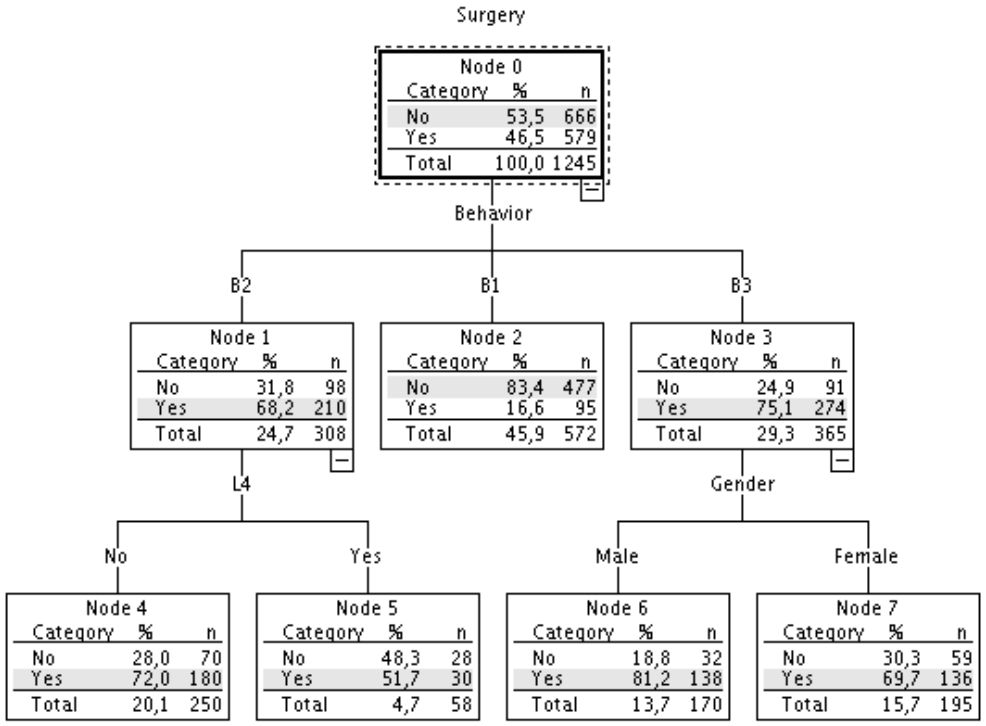
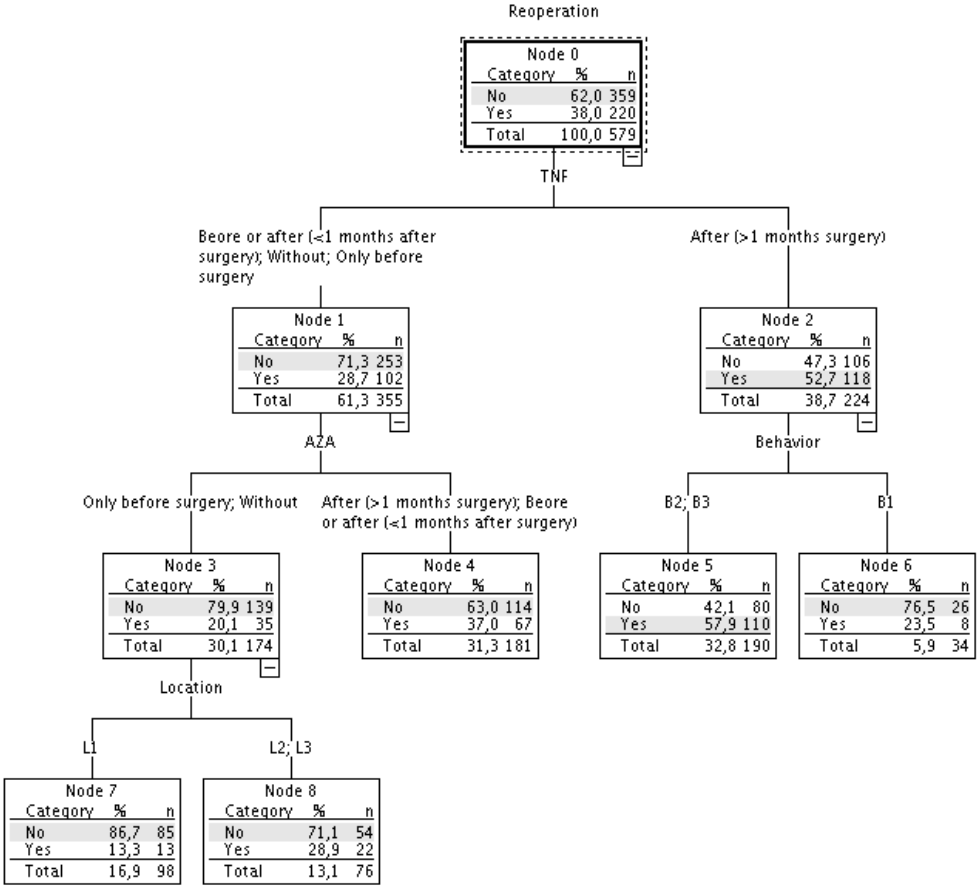


Figure 3- Decision tree for reoperation



6.2. THE RISK OF DISABLING, SURGERY AND REOPERATION IN CROHN'S DISEASE: A DECISION TREE-BASED APPROACH TO PROGNOSIS

Figure 4- Proportion and 95% confidence interval of outcome in derivation and validation cohort

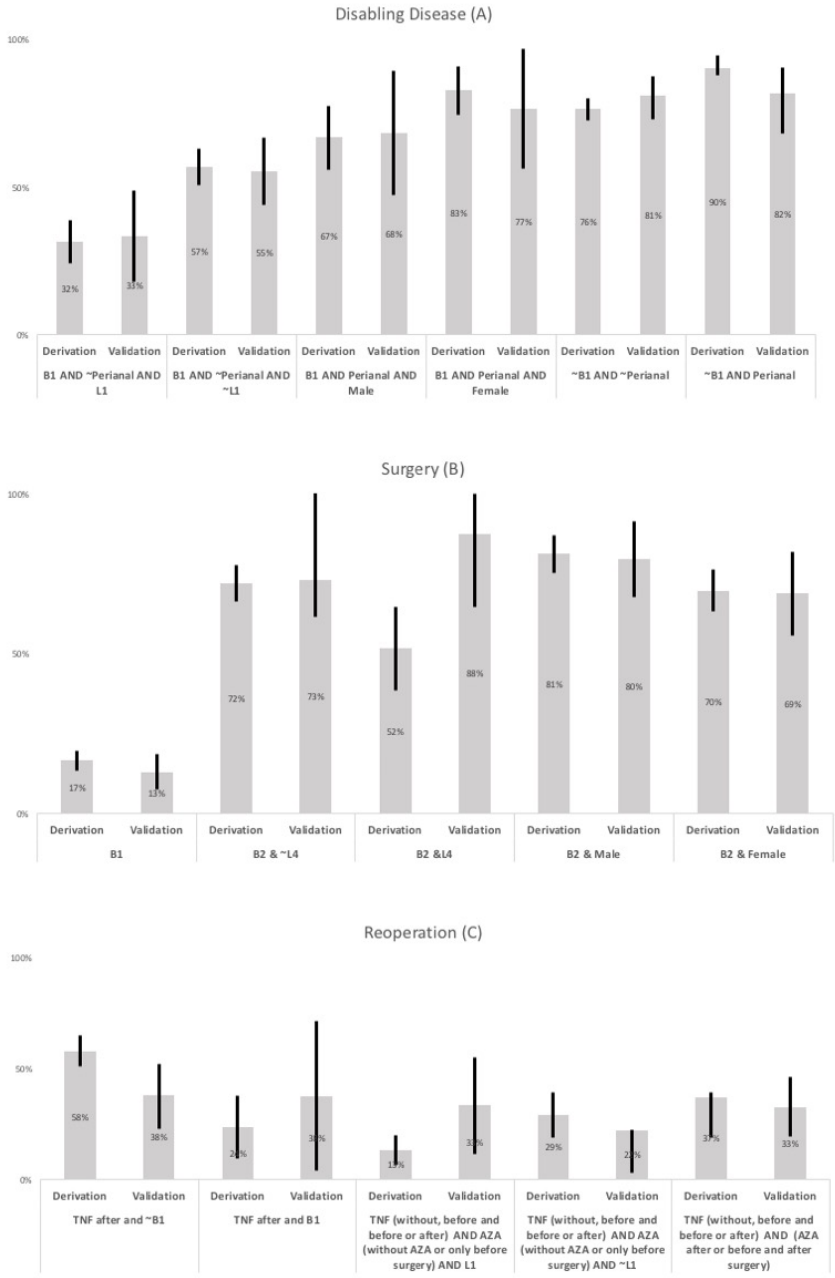
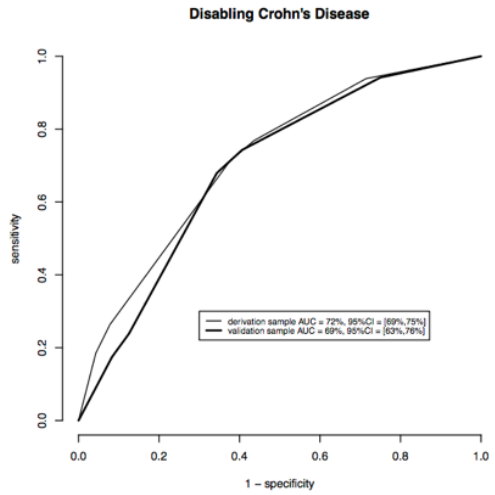
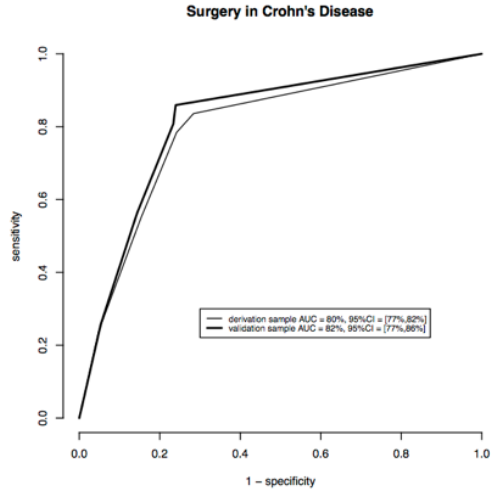


Figure 5- AUC


Disabling Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 72%, 95%CI = [69%,75%]
validation sample AUC = 69%, 95%CI = [63%,76%]


Surgery in Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 80%, 95%CI = [77%,82%]
validation sample AUC = 82%, 95%CI = [77%,86%]

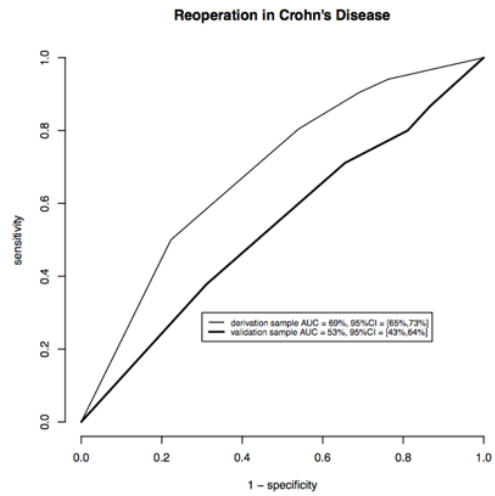
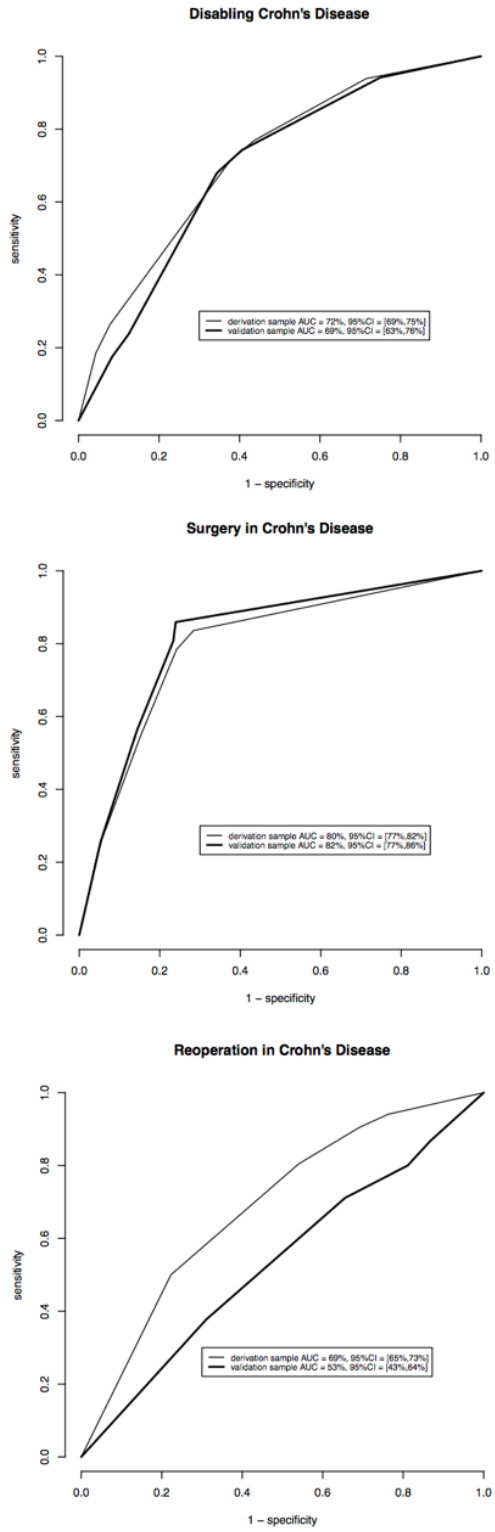

Reoperation in Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 69%, 95%CI = [65%,73%]
validation sample AUC = 53%, 95%CI = [43%,64%]

Figure 5- AUC


Disabling Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 72%, 95%CI = [69%,75%]
validation sample AUC = 69%, 95%CI = [63%,76%]
Surgery in Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 80%, 95%CI = [77%,82%]
validation sample AUC = 82%, 95%CI = [77%,86%]
Reoperation in Crohn's Disease
sensitivity
1 – specificity
derivation sample AUC = 69%, 95%CI = [65%,73%]
validation sample AUC = 53%, 95%CI = [43%,64%]

7. Discussion and recommendations

7. Discussion and recommendations

Being a chronic disease, and with non-curative therapeutic approaches, the prognosis of inflammatory bowel disease has a huge importance for both the patients and the clinicians. Given this, it is important to develop models which can predict the major outcomes with only few factors and as soon as possible. One of the most important groups of factors are clinical and demographical because they are easy to collect and do not depended on external methods, such as genetic or serologic ones. In recent years, different disease outcomes have been studied, namely disabling disease and reoperation for Crohns disease and colectomy for ulcerative colitis, and different factors were identified to be related with those outcomes. In this thesis, two systematic reviews with meta-analysis were developed to identify outcomes, and clinical and demographical factors which can predict those outcomes. In ulcerative colitis, the major event that may significantly affect the patients in terms of quality of life and mortality is colectomy [Baumgart and Sandborn, 2007]. The probability of having an abdominal surgery in these patients is around 25% in the first 10 years of the disease but half of them occur in the first year after diagnosis and colectomy rate is around 10%. Factors such as gender, smoking habits, disease extent, need for corticosteroids and hospitalization are all associated with colectomy [Dias et al., 2015].

7.1 Disabling disease

In Crohns disease, disabling disease was studied and factors such as age at diagnosis, perianal disease, location and initial use of steroids were isolated as independent prognostic factors [Dias et al., 2013]. However, the concept of disabling disease, introduced by Beaugerie et al.[Beaugerie et al., 2006] in 2006, is not consensual; in fact, disabling is a dynamic concept, which necessarily changes with the evolution of medical techniques and the different strategies followed to achieve disease control. Beaugerie et al.´s definition is the presence of at least one of the following criteria: two steroid courses required and/or steroid dependency; further hospitalisation after diagnosis or complications of the disease; chronic symptoms; immunosuppressive therapy; intestinal resection or surgical operation for perianal disease. This definition was used by Lolly et al. [Loly et al., 2008], in 2008 but, in 2011, Yang et al. [Yang et al., 2011] presented a study of disabling disease with the definition not including chronic symptoms. In our studies, we have chosen to use a stricter definition of global disabling disease, defining precise criteria: abdominal surgery, hospital admissions, course of steroids/year, steroid dependence or refractoriness, need to switch immunosuppressors or anti-TNF, and the appearance of new clinical events (abscesses, fistula, anal disease, stenosis). This change was motivated by the new concept of early starting immunosuppression, within a window of disease opportunity, instead of using it as the end of route. From our original studies of independent cohorts of Crohn´s patients, some clinical/demographical factors, as well as the impact of early approaches (surgery or immunosuppression), were identified as relevant for the studied outcomes.

The rate of disabling disease events were considerably high and did not differ between the two therapeutic choices (surgery: 77%, or immunosuppression: 76%, p=0.770). Concerning the surgical group there were no differences among patients with different immunosuppression starting points in the occurrence of disabling disease (p=0.372). The same scenario was observed in the immunosuppression group with no difference in the rate of disabling disease (p=0.487). When analysing the time to disabling disease adjusted to all variables (gender, age at diagnosis, location, behaviour, upper tract involvement and perianal disease) there were also no differences between the two groups (HR=0.963 [0.771-1.202]). This study shows that neither early surgery nor early immunosuppression can prevent the occurrence of disabling events in CD patients.

When we studied only patients with a surgical intervention, disabling disease was observed in 75% of the patients. Factors such as location (colonic disease: OR=2.615 [1.125-0.078]), upper tract involvement (OR=2.593 [1.125-6.078]) and a longer time elapsed from diagnosis to first surgery (13-36 months: OR=2.754 [1.538-4.934] and 36 months: OR=2.114 [1.318-3.235] presented a higher risk of disabling disease. Overall, the timing of therapeutic strategies affects the CD outcomes and an early surgery (within six months after diagnosis) can decrease the occurrence of disabling events.

Different prognostic models for disabling disease were derived using only clinical/demographical data. In the first one, Bayesian networks were used, achieving an AUC of 78% for the prognosis of disabling disease. Age at diagnosis, perianal disease, behavior and early therapeutic decision were found to be significant factors and used to create user-friendly matrices depicting the probability of having disabling disease, exhibiting good rule-in performance for the most important criteria: positive post-test odds=8.00 [2.72-23.44]. This value gives us improved safety in applying the matrices, since the odds of having disabling disease, having a positive test, are extremely high. A second model was developed, inducing a decision tree from the cohort data. The induced decision tree resulted in a three-level model of variables: first level included behavior phenotype, a two-way split with the risk of disabling for B1 (54%) apart from that of B2 and B3 phenotypes (80%); the second level considered the existence of perianal disease; location and gender were then included at the third level. Overall, patients with phenotypes B2 or B3 have a higher risk of disabling disease, while for phenotype B1, gender plays an important role, with female patients having a higher risk than males. Again this model exhibited good rule-in performance, with positive post-test odds of 4.24 [3.09-5.81]. The variables chosen by both methods were the same used in previous studies, showing the robustness of these algorithms [Beaugerie et al., 2006, Loly et al., 2008, Yang et al., 2011] and with good performance in the validation cohorts.

7.2 Surgery and Reoperation

Surgery has also an important impact in patients quality of life. Fifty percent of patients undergo surgery in the initial 10 years after diagnosis of CD [Carter et al., 2004, Peyrin-Biroulet et al., 2010], whereas a total of 80% is estimated to need surgery during the course of the disease [Moss, , Cosnes et al., 2002]. An induced decision tree, computed with all variables, resulted in a two-level model of variables: the first one included behavior phenotype, with different risk levels for B1 (16%), B2 (68%) and B3 (75%); the second level included information on upper track involvement (L4) and gender, i e, patients with a B3 phenotype have a higher risk of surgery than those with a B1 behavior, and this risk is further aggravated in male B3 patients. This model

exhibited good rule-out performance, with negative post-test odds for surgery of 0.15 [0.09-0.23], i.e. when the model predicts the absence of need for surgery, the odds of actually needing it are very low.

Recurrence, including reoperation, is also extremely frequent and affects 40% to 80% of CD patients [Bernell et al., 2000, Olaison et al., 1992]. Some clinical/demographical factors, as well as the impact of early approaches (surgery or immunosuppression), were identified and evaluated.

Concerning the impact of early approaches, our results show differences between surgery and immunosuppression approaches, and also relevant is the different time point at which the patients start immunosuppression therapy. When we studied only patients with the first abdominal surgery after diagnosis, the achieved rate of reoperation of 33% was the same as the value presented in a recent meta-analysis [Frolkis et al., 2014] for the 10-years risk of reoperation. Multiple risk factors patient-related, disease-related and surgery-related have already been identified and used to predict this outcome, but the literature is not consensual on this issue [Vaughn, 2014]. In our study, some risk factors were identified, namely age at diagnosis, disease phenotype, perianal disease and the introduction of pharmacological medication. A few studies have been published associating the introduction of medical therapeutics, namely immunosuppression, with reoperation. Immunosuppression was considered to be relevant in the CD management particularly when introduced before or after surgery as a prophylactic therapy [Vaughn, 2014]. Our study was not entirely conclusive in this regard, but highlighted the increased risk for patients beginning medical therapeutics only one month after surgery.

Different prognostic models for reoperation were also derived using only clinical/demographical data. In the first one (using Bayesian networks) achieved an AUC of 86% for the prognosis of reoperation. Age at diagnosis, perianal disease, behavior and early therapeutic decision were found to be significant factors and used to create user-friendly matrices depicting the probability of needing reoperation, exhibiting good rule-out performance for the most important criteria: negative post-test odds=0.02 [0.00-0.11]. This value gives us improved safety in applying the matrices, since the odds of needing reoperation, having a negative test, are extremely low. A second model was developed, also inducing a decision tree from the cohort data. The induced decision tree, computed with all variables plus therapeutics used during the disease, resulted in a three-level model of variables: first one included the moment of anti-TNF therapeutics, singling out those with more than 1 month after surgery (53% risk) from the remaining (29% risk); the second level included behavior (stratified in B1 vs B2/B3) and immunosuppression therapeutics, discriminating between those without or only before surgery, and the remaining; the third level considered disease location (L1 vs L2/L3). Overall, patients with a later introduction of pharmacological intervention (1 month after initial surgery) had a worse outcome, i.e, they have a higher probability of undergoing more than one surgery during the disease course. However, reoperation stood out as a harder outcome to predict, perhaps signalling a need for other factors to be included in the model, although negative post-test odds of 0.5 [0.24-1.01] suggests the model might nonetheless be useful to rule out patients.

7.3 Recomendation

Overall, clinical and demographical factors should be used more frequently in the prognosis of IBD because they are easier to collect than serologic or genetic ones. Factors such as age at diagnosis, behavior, perianal disease, and location are important predictors for negative outcomes and should, as soon as possible, be known.

Concerning interventions, immunosuppression, as the first therapy after diagnosis, is effective in preventing future surgeries, being its efficiency higher upon an early start. On the other hand, patients undergoing an early surgery after diagnosis have an increased tendency to be re-operated, even with a concomitantly early start of immunosuppression therapy. Given this, predictive models for CD prognosis could enhance the initial approach and, therefore, improve the clinical outcome. Likewise, models for ulcerative colitis must be developed using the same strategies and data. Finally, software or paper tools that could bring such models into bedside application are welcome and should be pursued, while cost-effectiveness studies should be run to evaluate the impact of such models/tools in clinical practice and in the prevention of new cases with negative prognosis.

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A. Preliminary study for a Bayesian net

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A.1 Preliminary study for a Bayesian network prognostic model for Crohn´s disease.

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Preliminary study for a Bayesian network prognostic model for Crohn's disease

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Abstract— **Crohn's disease is one type of inflammatory bowel disease whose incidence is currently increasing, and may affect any part of both the small and large intestine, possibly irritating deeper layers of the organs. Being a chronic disease, neither treatment nor surgery actually heals the patients. Thus, focus has been given to identifying good prognostic models based on clinical factors since they are more easily included in daily practice. The aim of this work is to provide an initial study on the adequacy of a Bayesian network model to enhance the prognosis prediction for patients with Crohn's disease. Multicentric study data of patients with surgery or immunosuppression in the six month after diagnosis was used to derive a Bayesian network, focusing on the prognosis and the analysis of factors interaction, including clinical features, disease course, treatment, follow-up plan, and adverse events. Two models were evaluated (naïve Bayes and Tree-Augmented Naïve Bayes) and also compared with logistic regression, using cross-validation and ROC curve analysis. Preliminary results showed competitive accuracy (above 75%) and discriminative power (above 70%). The generated models presented interesting insights on factor interaction and predictive ability for the prognosis, supporting their use in future clinical decision support systems.**

Keywords: prognosis; Crohn's disease; clinic decision support; Bayesian network models

I. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and progressive disease, subject to relapse and possibly disabling, with unknown etiology. Nonetheless, the interaction between genetic and environmental factors is also believed to play a role in both the etiology and pathogenesis of the disease, which can occur at any time in life but is usually diagnosed between the second an third decade of life [1].

The clinical course is usually characterized by intermittent relapses, with half the patients expressing a mild disease with low levels of relapse. The more aggressive cases usually require surgery [2] but, being a chronic disease, neither treatment nor surgery actually heals the patients, yielding frequent medical visits and hospitalizations, which in turn creates uncertainty about the professional and social future of patients and their families [3].

This is particularly true since in the last decades the medical treatment options have been dramatically changed. Other strategies are now approaching, namely accelerate step-up and top down treatment]. The top-down strategy is based on the very early use of intensive therapy (immunosuppressive and/or biologics) to maintain a good quality of life from the first flare-up of the disease and prevent any irreversible consequences [4]. Therefore, it is now crucial to identify simple clinical criteria at diagnosis to predict CD outcome.

Besides the classical approach of controlling the symptoms, recent studies have been focusing on quality of life improvement and hospitalization and surgery reduction. Since the treatment plan clearly affects the disease course, focus has been given to identifying good prognostic models based on genetic/serological and clinical/demographic factors, especially the latter since they are more easily included in daily clinical practice [5], [6].

But the studies developed to improve the prognosis have been struggling as the different published studies show heterogeneous results, likely the result of using different methodologies and/or applying different criteria for selection and evaluation. In addition, predicting the prognosis is a task of considerable uncertainty, so the development of predictive models also requires research. Although prognostic models are utterly required, they are, unfortunately, not widely studied. Moreover, the complicated nature of real-world biomedical data has made it necessary to look beyond traditional biostatistics [7] without losing the necessary formality. For example, naive Bayesian approaches are closely related to logistic regression [8]. Bayesian statistical methods allow taking into account prior knowledge when analyzing data, turning the data analysis into a process of updating that prior knowledge with biomedical and health-care evidence [9], which offers a general and versatile approach to capturing and reasoning with uncertainty in medicine and health care [7]. On a general basis, a Bayesian network represents a joint distribution of one set of variables, specifying the assumption of independence between them, with the inter-dependence between variables being represented by a directed acyclic graph [10], and their

A.1. PRELIMINARY STUDY FOR A BAYESIAN NETWORK PROGNOSTIC MODEL FOR CROHN´S DISEASE.

applicability to other clinical domains – with high levels of uncertainty – has been already widely studied [11] and present thus a valuable approach for studying disabling in the context of Crohn's disease.

The aim of this work is to initiate the study of developing Bayesian networks for the predictive prognosis of patients with Crohn's disease.

II. MATERIAL AND METHODS

Multicentric study data of Crohn's patients with surgery or immunosuppression in the first six months after diagnosis with more than 18 years old and at least 3 years of follow were included. A total of 591 patients were included (out of 668 patients collected). Seventy-seven patients were excluded because of missing values.

A. Studied variables and outcomes

Data collection included the characterization of patient and illness (data of diagnosis, data of surgery or immunosuppression, gender, age at diagnosis, disease location, behavior and presence of perianal disease), follow-up data (total number of surgeries and hospitalization; treatment, namely corticoids, immunosuppressives or ANTI-TNF and adverse events - stenosis, abscess, perforation and anal disease). The variable event was calculated after data collection to express the happening of surgery, surgery in the first 6 months after diagnosis and immunossupressives up to 2 months after surgery, surgery and immunossupressives more than 2 months after surgery and immunossupressives in the first 6 months after diagnosis.

The main outcome of this study was disabling disease defined by the presence of at least one of the following criteria: more than one surgery (excluding the first); more than two hospitalizations (excluding the first); two steroids course requirements per year, steroids dependency, steroids refractory; need to switch immunosuppressives or Anti-TNF therapy; adverse events.

B. Model building and evaluation

Logistic regression was applied to all studied variables to predict disabling. Additionally, two Bayesian network classifiers were built – Naïve Bayes (NB) and Tree Augmented Naïve Bayes (TAN) – which differ on the number of conditional dependences (besides the outcome) allowed among variables (NB: zero dependences; TAN: one dependence), in order to choose the structure which could better represent the problem.

To assess the general structure and accuracy of learned models, stratified 10-fold cross-validation was repeated 10 times, estimating accuracy, sensitivity, specificity, precision (positive and negative predictive values) and the area under the ROC curve, for all compared models.

Logistic regression was applied with R package *stats* [12], Bayesian network structure was learned with WEKA software [13], Bayesian network parameters were estimated with R package *gRain* [14], and ROC curves were computed with R package *pROC* [15].

TABLE I. MAIN CHARACTERISTICS OF PATIENTS WITH CROHN'S DISEASE INCLUDED IN THE STUDY.

	n	(%)
Event		
E1 – surgery	87	(15%)
E2 – surgery and IMUNO<2 months	42	(7%)
E3 – surgery and IMUNO>2 months	194	(33%)
E4 - imuno	268	(45%)
Gender		
Male	279	(47%)
Female	312	(53%)
Age at diagnosis		
A1 (<=16 years)	34	(6%)
A2 (17-39 years)	425	(72%)
A3 (>=40 years)	132	(22%)
Location		
L1 – Ileal	274	(46%)
L2 – Colonic	58	(10%)
L3 – Ileocolic	259	(44%)
L4 upper		
No	528	(89%)
Yes	63	(11%)
Behaviour		
B1 – Non structuring/non penetrating	176	(30%)
B2 – Structuring	212	(36%)
B3 - Penetrating	203	(34%)
Perianal disease		
No	440	(74%)
Yes	151	(26%)
Disabling disease		
No	158	(27%)
Yes	433	(73%)

III. RESULTS

The main characteristics of patients are shown in Tab. I. Forty five percent of patients made immunossupressives in the first 6 months after diagnosis and only 15% had surgery. Fifty three percent were female and only 6% had less than 16 years old. Concerning location 46% had ileal disease and 34% had penetrating disease. We observed that 73% of patients had disabling during the course of the disease.

A. Bayesian network model qualitative analysis

Fig. 1 and 2 show the resulting qualitative models, where we can better inspect the additional dependencies introduced by the TAN model. It is interesting to note the association between behavior and perianal disease, location, age and event. Perianal disease was also associated with gender while event was associated with L4.

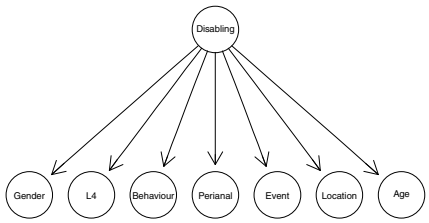

Figure 1. Naïve Bayes

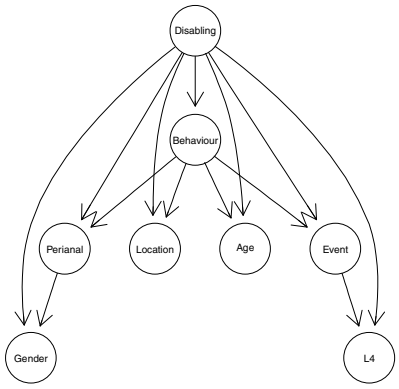

Figure 2. Tree-Augmented Naïve Bayes

B. *Bayesian network model in-sample analysis*

Fig. 3 and 4 present the in-sample ROC curves for NB and TAN models, respectively, where no specific cut off rises from the curves' shape. Resulting AUC were 78.1% (NB) and 79.5% (TAN).

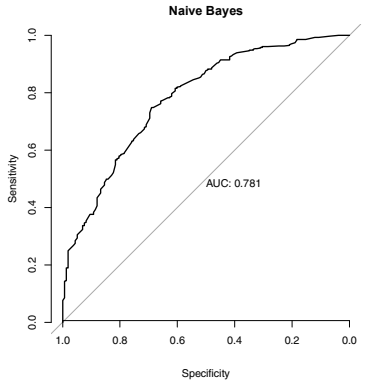

Figure 3. In-sample ROC curve for Naïve Bayes

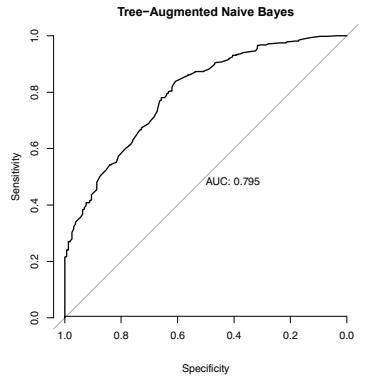

Figure 4. In-sample ROC curve for Tree-Augmented Naïve Bayes

C. *Evaluation with cross-validation*

Aggregated results from 10 times 10-fold cross validation for both models are presented in Tab. II. Both classifiers presented good accuracy levels (>75%) and discriminative power (AUC > 70%). TAN approach presented a lower ability to identify patients with disability (91% vs 95%), although expressing similar precision during prediction (81% vs 79%). On the other hand, regarding patients without disabling, TAN revealed higher ability to identify them (40% vs 32%) at the cost of a lower precision for these cases (62% vs 70%).

TABLE II. CROSS-VALIDATION RESULTS FOR PREDICTING DISABLING IN CROHN'S DISEASE, USING LR, NB AND TAN MODELS.

	LR % [CI95%]	NB % [CI95%]	TAN % [CI95%]
Accuracy	76.18 [75.21,77.16]	78.09 [77.12,79.06]	77.31 [76.32,78.3]
Sensitivity	83.38 [82.20,84.45]	94.85 [94.20,95.50]	90.83 [89.99,91.66]
Specificity	56.60 [54.24,58.96]	32.37 [30.21,34.52]	40.40 [38.18,42.61]
Precision (PPV)	84.18 [83.33,85.03]	79.34 [78.30,80.38]	80.67 [79.62,81.71]
Precision (NPV)	55.81 [53.83,57.78]	70.17 [66.78,73.57]	61.90 [59.01,64.8]
AUC	76.64 [53.83,77.91]	76.35 [74.98,77.73]	74.33 [72.83,75.83]

IV. DISCUSSION

The main contribution of this work is the preliminary study for the development of graphical representation models of uncertain knowledge existent in the characterization of disabling disease.

From the qualitative models presented earlier, several associations improved the naïve approach. The disease behavior (whether it is penetrating or presenting stenosis or neither) appears to be directly associated with perianal disease (better for patients with perianal disease, which is, in turn, associated with male gender), location of the disease, event (also associated with L4) and age at diagnosis (worse behavior for older patients). This representational strategy allows an easy visualization of the model, reinforcing the experts with the possibility of a supported decision, not only by risk factors or discriminating cut points, but mostly supported in the interdependences of studied variables and their causality.

From the quantitative analysis, the most relevant aspect of the proposal is that no significant decrease in predictive accuracy rises from the enhancement of graphical analysis of factor dependences, enabling a sound inspection by the clinical experts. Furthermore, we may note that the Tree-Augmented Naïve Bayes might have over-adjusted to the training cohort (i.e. higher in-sample AUC), losing some generalization ability (i.e. lower quality on cross-validation), but this is yet to be confirmed with further validation with independent cohorts.

A.1. PRELIMINARY STUDY FOR A BAYESIAN NETWORK PROGNOSTIC MODEL FOR CROHN´S DISEASE.

V. CONCLUSIONS

This study showed a preliminary approach of Bayesian networks for prognosis in Crohn's disease. These results show good performance indications, reinforcing the path of developing probabilistic graphical models for future inclusion in clinical decision support systems.

Future directions include the analysis of expert-designed causal models, hill-climbing greedy strategies for structure learning, and temporal Bayesian networks for the modeling of temporal interdependences useful for mid- and long-term prognosis of Crohn's disease course.

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B. Building the Bayesian net

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B.1 Disabling and reoperation in patients with Crohn´s disease subject to early surgery or immunosuppression: A Bayesian network prognostic model. disease.

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Disabling and reoperation in patients with Crohn's disease subject to early surgery or immunosuppression: a Bayesian network prognostic model

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Abstract— Crohn's disease is one type of inflammatory bowel disease whose incidence is currently increasing, subject to relapse and disabling, with unknown etiology, and usually diagnosed between the second and third decade of life. The aim of this work is to develop a Bayesian network tool to predict disabling and reoperation in patients with Crohn's disease subject to early surgery or immunosuppressors intake. Multi-centric study data from patients with surgery or immunosuppression in the first six months after diagnosis was used, focusing on the prognosis and the analysis of factors' interaction. Patients were grouped by the index episode: immunosuppressors intake, and surgery (stratified considering the use or not of immunosuppressors 6 months after surgery). Patient group was associated with disease behavior, upper gastrointestinal tract location (L4) and age at diagnosis, while disease extent was associated to perianal disease. For disabling, association between perianal disease and gender and location was also found. Association between gender and L4 was also found for reoperation. The cross-validated discriminative power of the models were high for both disabling (above 70%) and reoperation (above 80%). The generated models presented interesting insights on factor interaction and predictive ability for the prognosis, supporting their use in future clinical decision support systems.

Keywords: prognosis; Crohn's disease; clinic decision support; Bayesian network models

I. INTRODUCTION

Crohn's disease is a chronic illness with unknown etiology usually diagnosed during the second and third decade of life. The interaction between genetic and environment factors had a important role in the etiology of the disease [1].

The disease could had along periods of remission but the more aggressive cases requires more aggressive interventions like surgery [2] but, being a chronic disease, neither treatment nor surgery actually heals the patients, yielding frequent medical visits and hospitalizations, which in turn creates uncertainty about the professional and social future of patients and their families [3].

The treatment of Crohn's disease has changed in the last decades. Strategies like step-up or top down treatments have been more frequently chosen. The top-down strategy is based on the very early use of intensive therapy (immunosuppressive and/or biologics) to maintain a good quality of life from the first flare-up of the disease and prevent any irreversible consequences [4].

In our day the principal focus of treatment has been the improvement of quality of life, reduction of surgeries or hospitalization, besides the sole control of symptoms. Since the treatment plan clearly affects the disease course, focus has been given to identifying good prognostic models based on clinical/demographic factors since they are more easily included in daily clinical practice [5], [6].

However, prognostic studies show heterogeneous results, likely as a result of using different methodologies and/or applying different criteria for selection and evaluation. In addition, predicting the prognosis is a considerably uncertain task, so the development of predictive models also requires research. Also, traditional biostatistics is no longer enough to cope with the real-world biomedical data and it is necessary to look to other techniques [7]. Bayesian networks are a good choice since they deal well with prior knowledge, collected in published evidence included in quality literature or in primary or secondary data sources, and transform the data analyses in a process of updating the prior knowledge with available evidence at inference time [9], dealing better than other models with the uncertainty in the data. Bayesian networks are represented by a qualitative model (which describes the relations among variables) and a quantitative model (which gives the joint probability of all variables) which allows the inspection of marginal probabilities for each variable's state, and their use in the computation of a posteriori probabilities for single patients at inference time [10].

A preliminary study on the problem constituted a proof-of-concept for the use of Bayesian network classifiers as prognostic predictor model for disabling of prognostic prediction of disabling [15]. However, a thorough follow-up clinical appraisal of those results revealed that the analysis of immunosuppressive therapy prior to six months after surgery was misleading, so a new definition of groups should be

considered. Also, an additional important outcome should be modelled, as clinicians usually consider the risk for reoperation as a decisive factor for defining the best intervention for those patients.

The aim of this work is to develop Bayesian networks for the predictive prognosis of patients with Crohn's disease subject to early surgery or immunosuppression, namely targeting disabling disease and reoperation.

II. Material And Methods

Multi-centric study data of Crohn's patients with surgery or immunosuppression in the first six months after diagnosis with more than 18 years old and at least 3 years of follow were included. A total of 489 patients were included (out of 668 patients collected). Hundred and seventy-nine patients were excluded because of missing values.

A. Studied variables and outcomes

This study was a retrospective study and the collected variables included: characterization of patients (gender), disease (data of diagnosis and intervention (surgery and/or immunosuppressors, location with or not upper gastrointestinal tract, behavior and perianal disease), and follow up data (namely number of surgery and hospitalizations, treatments and adverse events). Patients were grouped by the index episode: immunosuppressors intake, and surgery (stratified considering the use or not of immunosuppressors 6 months after surgery).

The two main outcomes were disabling (defined by the presence of at least one of the following criteria: more than one surgery, excluding the first; more than two hospitalizations, excluding the first; two steroids course requirements per year, steroids dependency, steroids refractory; need to switch immunosuppressors or Anti-TNF therapy; adverse events) and reoperation (defined by the deed of second surgery).

B. Model building and evaluation

Following the preliminary study presented previously [15], Tree Augmented Naïve Bayes (TAN) models were derived using all studied variables to predict disabling and reoperation. To assess the general structure and accuracy of learned models, stratified 10-fold cross-validation was repeated 10 times, estimating accuracy and the area under the ROC curve.

WEKA software [12] was used to learn the Bayesian network structure. gRain [13] and pROC [14] R packages were also used to estimate de parameters of the networks and ROC curves, respectively.

III. Results

The main characteristics of patients are shown in Tab. I. Forty-eight percent of patients took immunosuppressors in the first 6 months after diagnosis and 36% had surgery with immunosuppressors 6 months after surgery. Forty-six percent were male and 21% had more than 40 years old at diagnosis. Concerning location 47% had ileal disease and 32% had penetrating disease. We observed that 64% of patients had disabling during the course of the disease and 18% needed a second surgery.

TABLE I. Main characteristics of patients with Crohn's disease included in the study (n=489).

	n	(%)
Event		
S_0 surgery	80	(16%)
S_I surgery and immuno > 6 mo after surgery	175	(36%)
I immunosuppression	234	(48%)
Gender		
Male	225	(46%)
Age at diagnosis		
A1 & A2 (<40 years)	388	(79%)
A3 (>=40 years)	101	(21%)
Location		
L1 Ileal	232	(47%)
L2 Colonic	45	(9%)
L3 Ileocolic	212	(43%)
L4 upper		
Yes	55	(11%)
Behavior		
B1 Non structuring/non penetrating	158	(32%)
B2 Structuring	176	(36%)
B3 Penetrating	155	(32%)
Perianal disease		
Yes	125	(26%)
Disabling disease	314	(64%)
Reoperation	89	(18%)

A. Bayesian network model qualitative analysis

The qualitative models were show in Fig 1 and 2. Patient group was associated with disease behavior, upper gastrointestinal tract location (L4) and age at diagnosis, while disease extent was associated to perianal disease.

For disabling, association between perianal disease and gender and location was also found. Association between gender and L4 was also found for reoperation.

B. Bayesian network model validation

Fig. 3 presents the in sample, leave-one-out and 10 times 10-fold cross validation ROC curves for disabling and reoperation models, respectively. Resulting validation AUC were between 72% and 73%. (for disabling) and between 79% and 80% (for reoperation).

IV. Discussion

The main contribution of this work was the development of prognostic models for disabling disease and reoperation. This models were developed after a preliminary study [15] done for the adequacy of these techniques into this problem, where comparison with other methods, namely logistic regression, has been assessed. Other clinical problems were also already addressed in the past with good performance, easy interpretation and friendly representations [7], [8], [11].

From models presented in Fig. 1 and 2 it was possible to infer some known clinical associations. In both outcomes, patient group was associated with disease behavior (whether it is penetrating or presenting stenosis or neither), upper gastrointestinal tract location (L4) and age at diagnosis, while disease extent was associated to perianal disease. These global dependencies show a common thread for knowledge representation in Crohn's disease management, specifically tune for each outcome considering the added associations between perianal disease and gender and location (found for disabling) and the association between gender and L4 (found for reoperation).

This knowledge representation allows an easy visualization of the model, supporting the experts' decision beyond the use of risk factors and discriminative cut points, into a support on the interdependences of studied variables and their induced causality.

From the quantitative analysis, and following the discussion from previous preliminary study - which showed that no significant decrease in predictive accuracy rises (beyond the naïve Bayes approach) with the enhancement of graphical analysis of variables' dependences - the Tree Augmented Naïve Bayes proved to be an accurate prognostic model, usable in clinical settings, even though it might (as expected) slightly over fit the training cohort (i.e. higher in-sample AUC), losing some generalization ability (i.e. lower quality on cross-validation). Further analysis shall confirm such suspicions using independent cohorts.

V. Conclusions

The cross-validated evaluation of the Bayesian network classifiers derived in this study resulted in high accuracy and discriminative power for both disabling (above 70%) and reoperation (above 80%) outcomes in Crohn's disease patients subject to early surgery or immunosuppression. The generated models presented interesting insights on factor interaction and predictive ability for the prognosis, supporting their use in future clinical decision support systems.

Current path of research includes the definition of clinically usable decision support tools, based on the hereby derived Bayesian network classifiers and temporal Bayesian networks for the modeling of temporal interdependences useful for mid- and long-term prognosis of Crohn's disease course, taking into account the specific modeling of immunosuppressors intake.

Acknowledgment

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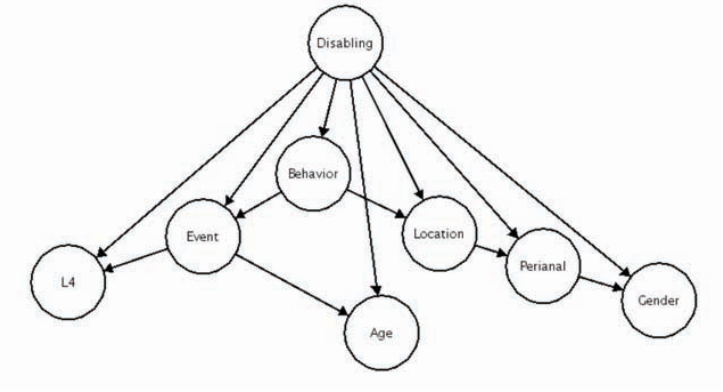

Figure 1. Modeling disabling in Crohn's disease patients subject to early surgery or immunosuppression – Tree Augmented Naïve Bayes

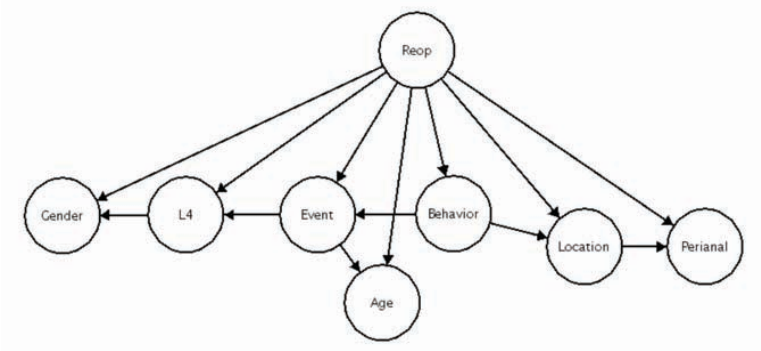

Figure 2. Modeling reoperation in Crohn's disease patients subject to early surgery or immunosuppression – Tree Augmented Naïve Bayes

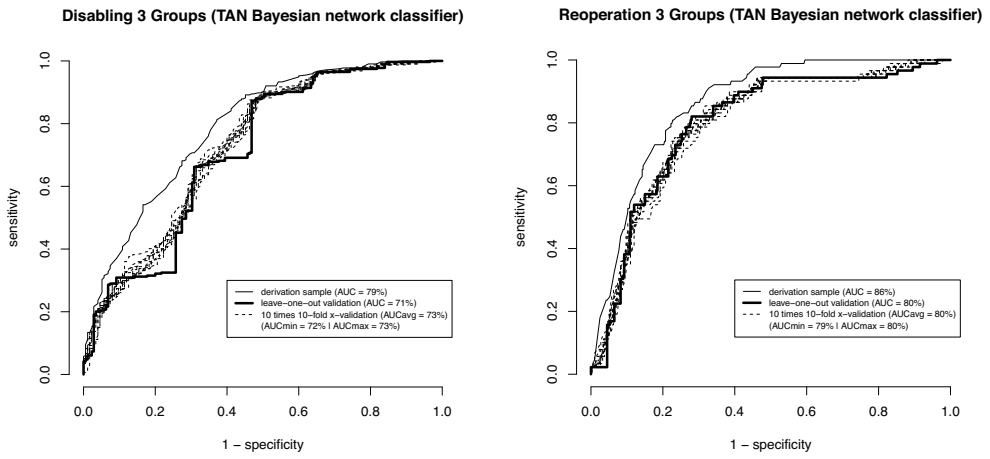

Figure 3. In sample , leave-one-out and 10 cross validation ROC curves of TAN models for disabling and reoperation outcomes.

C. Using the Bayesian net

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CrohnBayes Online Clinical Decision Tool

This appendix presents screenshots of **CrohnBayes** (Figure C.1), an online clinical decision tool for direct Bayesian network inference, which queries the models built in this thesis, providing the user with:

Figure C.2 an estimate of the risk for a subgroup of patients, or a patient with missing observations.

Figure C.3 an individualized risk estimate for the patient, having all included variables been observed.

CrohnBayes was developed with the invaluable help of Raphael Oliveira and Pedro Pereira Rodrigues.

The most recent (beta) version of the tool is available for academic review at

`http://servicosforms.gim.med.up.pt/form_test/crohnbayes.html`

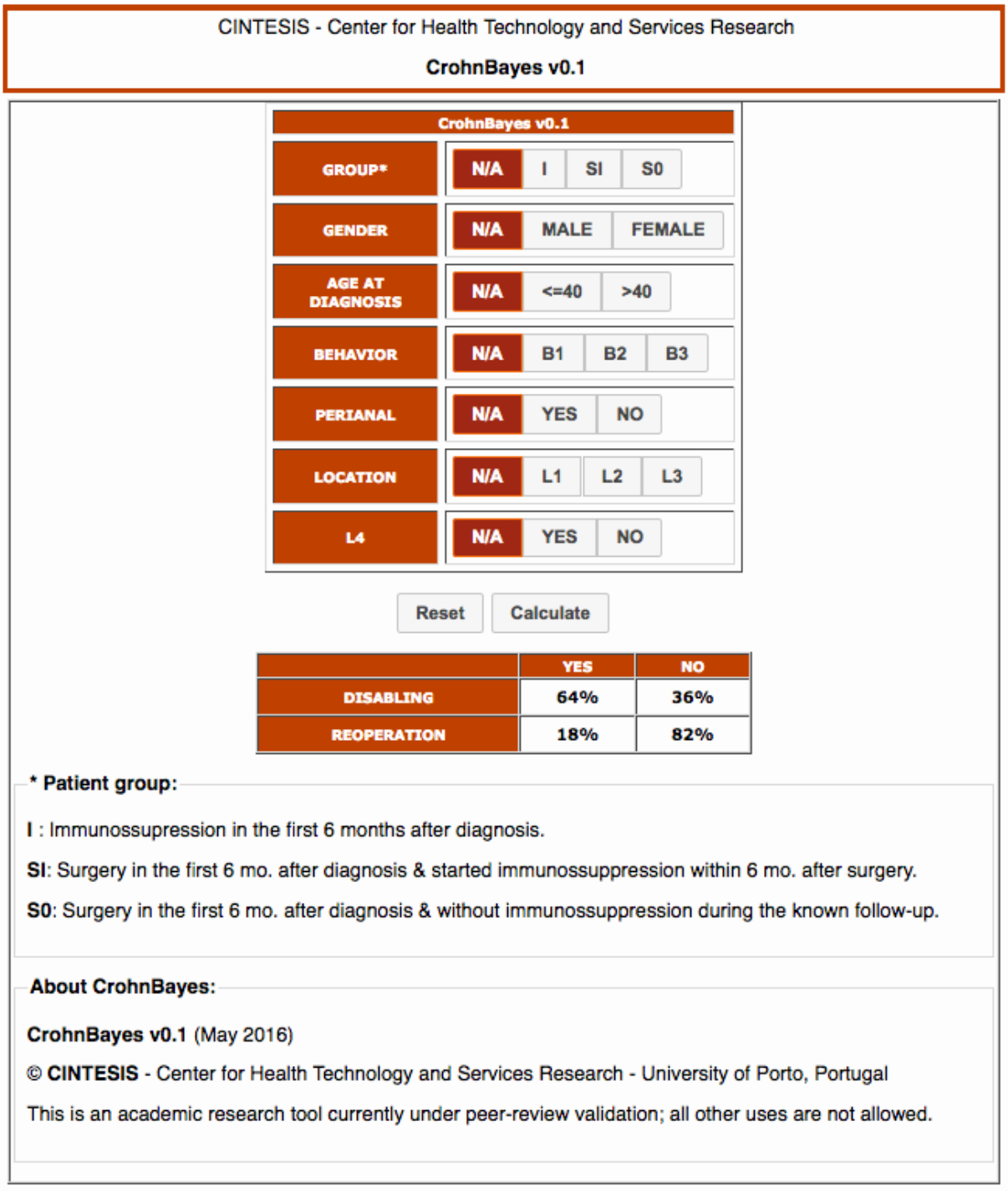

Figure C.1: CrohnBayes: Online clinical decision tool

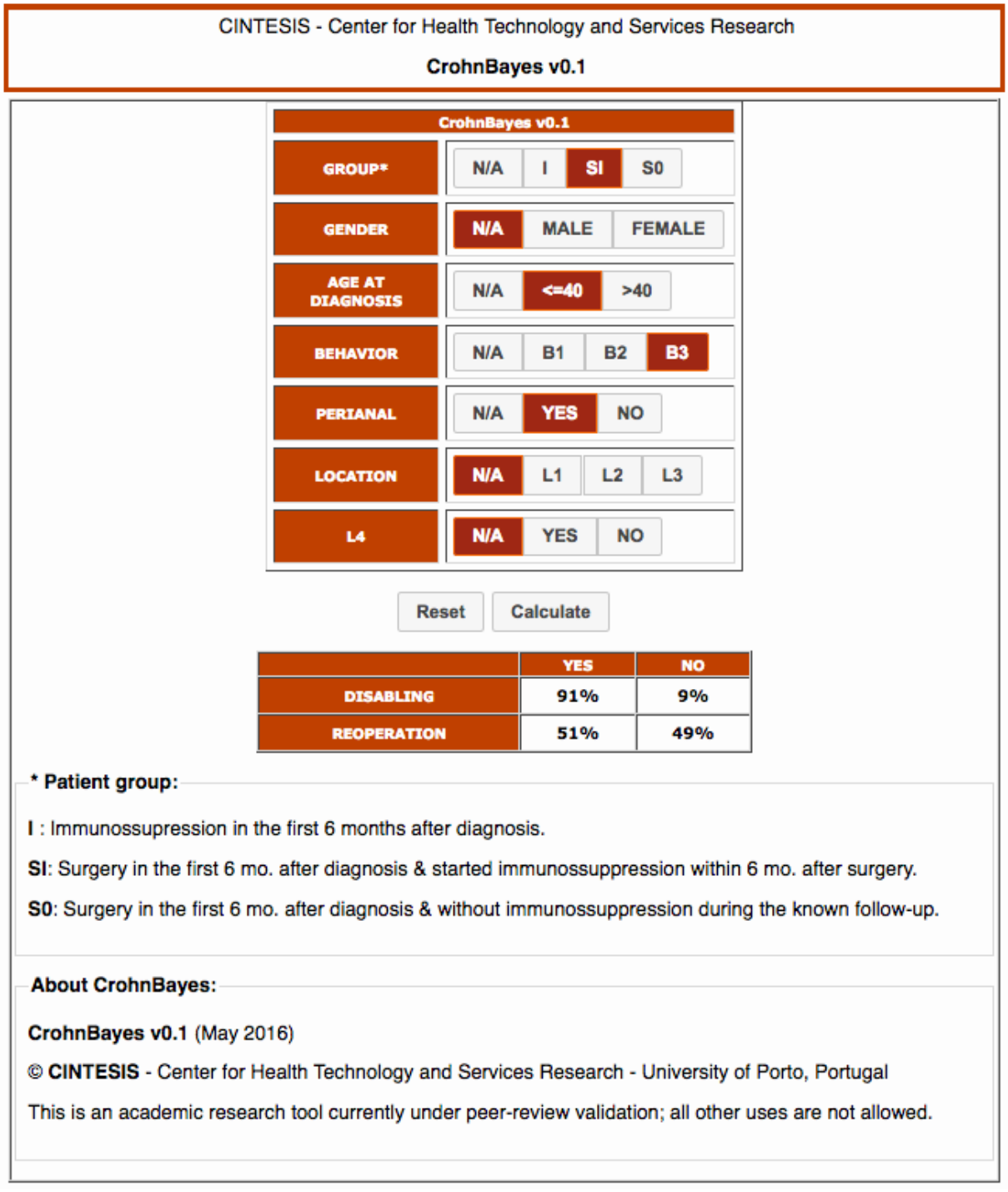

Figure C.2: CrohnBayes: Example of use with missing observations

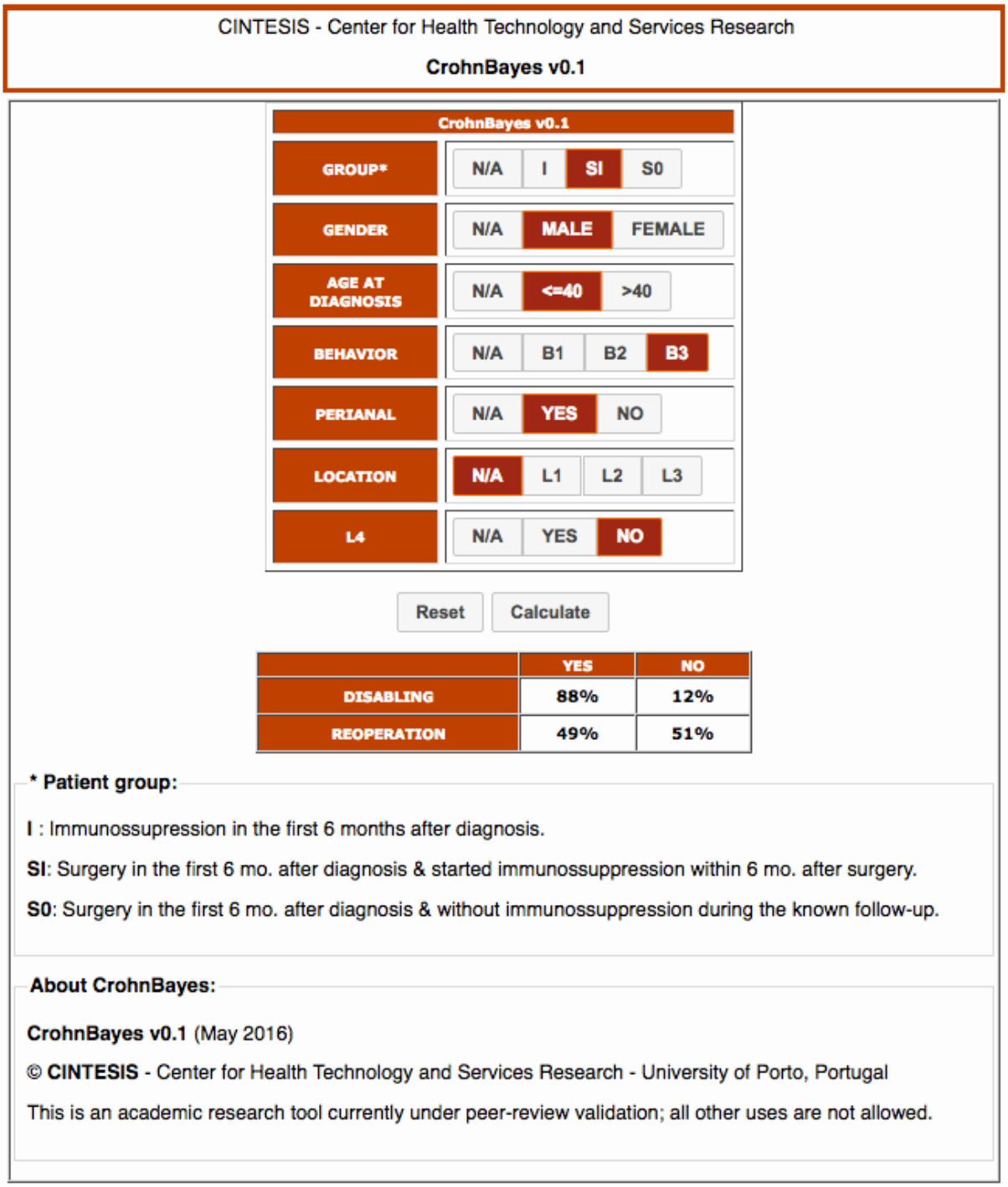

Figure C.3: CrohnBayes: Example of use with all included variables