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# The Risk of Developing Disabling Crohn's Disease: Validation of a Clinical Prediction Rule to Improve Treatment Decision Making

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**Keywords**
Crohn's disease · Personalized medicine · Biomarkers · Predictive factors · Risk factors · Natural history

**Abstract**

***Background:*** Crohn's disease (CD) is characterized by the development of complications over the course of the disease. It is crucial to identify predictive factors of disabling disease, in order to target patients for early intervention. We evaluated risk factors of disabling CD and developed a prognostic model. ***Methods:*** In total, 511 CD patients were retrospectively analyzed. Univariate and multivariate logistic regression analyses were used to identify demographic, clinical, and biological risk factors. A predictive nomogram model was developed in a subgroup of patients with noncomplicated CD (inflammatory pattern and no perianal disease). ***Results:*** The rate of disabling CD within 5 years



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after diagnosis was 74.6%. Disabling disease was associated with gender, location of disease, requirement of steroids for the first flare, and perianal lesions. In the subgroup of patients (310) with noncomplicated CD, the rate of disabling CD was 80%. In the multivariate analysis age at onset <40 years (OR = 3.46, 95% confidence interval [CI] = 1.52–7.90), extensive disease (L3/L4) (OR = 2.67, 95% CI = 1.18–6.06), smoking habit (OR = 2.09, 95% CI = 1.03–4.27), requirement of steroids at the first flare (OR = 2.20, 95% CI = 1.09–4.45), and albumin (OR = 0.59, 95% CI = 0.36–0.96) were associated with development of disabling disease. The developed predictive nomogram based on these factors presented good discrimination, with an area under the receiver operating characteristic curve of 0.723 (95% CI: 0.670–0.830). ***Conclusion:*** We identified predictive factors of disabling CD and developed an easy-to-use prognostic model that may be used in clinical practice to help identify patients at high risk and address treatment effectively.



## Introduction

Crohn's disease (CD) is a progressive chronic inflammatory condition that primarily affects the gastrointestinal tract. It is characterized by the development of complications over the course of the disease [1, 2], mainly strictures and fistulas, that lead to persisting and refractory symptoms and ultimately surgery [3]. These symptoms can have substantial psychosocial implications, with a consequent impact on the overall quality of life of patients [4].

The complex etiopathogenesis of the disease remains largely unknown, but it has been suggested that it is multifactorial, including genetic, environmental, immunological, and infectious factors [5, 6]. The growing understanding of the mechanisms underlying the development of CD has led to significant advances in the ability to treat the disease more effectively. Still, CD is not medically or surgically curable and patients require lifelong therapeutic approaches.

Until recently, therapy for CD has been based on a "step-up" approach that focuses on inducing clinical remission with a progressive intensification of the treatment as the disease severity increases. According to this approach, biological therapies such as antitumor necrosis factor agents are administered after the failure of steroids and immunosuppressants [7, 8]. However, current treatment strategies are aimed not only at controlling symptoms but also at preventing disease progression and improving long-term outcomes for patients, while minimizing short- and long-term adverse events [9–12]. Several studies have suggested that "top-down" strategies consisting on the early introduction of intensive therapies with biological agents – e.g., antitumor necrosis factor drugs – and immunosuppressive drugs, can modify the natural history of the disease [11–13]. Nevertheless, the course of CD varies considerably from individual to individual and the exact point at which immunosuppressants and/or biologics should be initiated is not clear [14]. In fact, half of CD patients will have pure inflammatory, uncomplicated disease in the long-term, and up to 10–20% will have sustained remission without maintenance therapy [15]. These findings indicate that a "top-down" approach cannot be recommended in all newly diagnosed CD patients because of the risk of overtreatment among those who are likely to have a benign disease course. Overtreatment also implies a greater risk of developing some other diseases or adverse events and generates unnecessary costs. On the contrary, patients who could benefit of this "top-down" strategy would be those at elevated risk of suffering disabling disease [16]. Thus, identification of factors predicting a severe course of CD at diagnosis is essential for the design of new treatment algorithms that could change the natural course of the disease [17, 18]. In recent years, precision medicine encompassing a multitude of data-driven and multi-omic approaches has been explored to foster accurate clinical decision making [19]. However, the implementation of these techniques can be very costly and difficult to implement in standard management of patients, and gastroenterologists still base their treatment strategies primarily on the clinical characteristics.

The most common risk factors associated with the development of disabling CD, apart from genetic and serological factors, are clinical, environmental, and endoscopic parameters. Specifically, the most prevalent clinical parameters confirmed as predictive markers for developing disabling disease at 5 years are an age below 40 years, the need for steroid treatment during the first flare and the presence of perianal lesions [16, 20, 21]. Other risk factors include small bowel involvement, stricturing disease, ileocolonic location, the presence of extraintestinal manifestations, and a history of smoking [22–27]. All these factors could be used in helping clinicians to tailor therapy, and therefore improve the clinical outcome of patients at a higher risk of developing disabling disease.

In this study, we aimed to confirm variables predictive of a disabling course already established in previous works. We also evaluated additional potential risk factors of developing disabling disease in patients with noncomplicated CD at diagnosis and developed and validated a nomogram prognostic model.

## Materials and Methods

*Study Design*

A retrospective, nationwide, multicenter study was performed in 16 hospitals in Spain. This study was designed and supported by the young group of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). Each participating center retrieved data from the ENEIDA (Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales [Spanish National Study on Inflammatory Bowel Disease: Genetic and Environmental Determinants]) database. ENEIDA is a registry of the GETECCU, which includes patients with inflammatory bowel disease (IBD) and records prospectively clinical characteristics, outcomes, and treatments [28]. The ENEIDA registry was approved by the Hospital Clínic de Barcelona Ethics Committee in 2006 ("Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona," ref. 2006/3155), and its use by the participating centers complies with all local and national regulations. All patients included in the registry signed an informed consent document authorizing the use of their clinical data for research purposes. The study was conducted in accordance with the Declaration of Helsinki.

*Data Collection and Definitions*

Demographic and clinical data were retrospectively and anonymously retrieved from clinical records of outpatients admitted at the participating centers with a definite diagnosis of CD, according to Lennard Jones' criteria [29]. Patients were aged 18 years and older, with a follow-up of at least 5 years after diagnosis and a complete medical record. Patients who underwent surgical procedures or started either immunosuppressive (azathioprine, 6-mercaptopurine, or methotrexate) or biological therapies at diagnosis or within the first month after diagnosis were excluded from the study.

Baseline characteristics obtained at the time of the first diagnosis included gender, age at disease onset (group A1 [<17 years old], group A2 [17–40 years old], and group A3 [>40 years old]); disease location at diagnosis (according to the Montreal's classification [30]); behavior at diagnosis (according to the Montreal's classification [30]); previous appendectomy, smoking status (current smoker if > 1 cigarette/day, vs. non- or ex-smoker); use of steroids to treat the first flare-up; perianal lesions at diagnosis; extraintestinal manifestation at diagnosis; family history of IBD; and fever (>38°C at diagnosis). We also used the following biological biomarkers: hemoglobin, C-reactive protein (CRP), and albumin.

Disabling CD was defined according to the definition used in the study performed by Beaugerie et al. [16]. Hence, CD was considered as disabling when at least one of the following criteria was present: requirement of more than two steroid courses and/or dependence on steroids; further hospitalization after diagnosis for the first flare-up or complication of the disease (strictures, fistulas, and abscesses; intestinal neoplasia; need for surgery; and hospitalizations); need for immunosuppressive and/or biological therapy; and intestinal resection or surgical operation for perianal disease. On the other side, to be adequately classified as having a non-disabling disease within the 5-year period following diagnosis, patients needed to have a complete 5-year follow-up and not manifest any criterion of disabling disease during this time interval.

Patients with noncomplicated CD at diagnosis were considered those with a non-stricturing non-fistulizing disease behavior (B1) according to the Montreal's classification [30], and who did not suffer from perianal disease.

*Predicting Factors and Statistical Analysis*

Continuous variables are presented as mean and standard deviation and were analyzed using Student's *t* tests. Categorical variables are presented as percentages or proportions and were analyzed using the $\chi^2$ or the Fisher's exact test. Associations between each of the prognostic variables and the development of disabling CD with time were assessed using univariate analysis. These variables were gender; age at diagnosis (below 40 years, equal to or above 40 years); location of the disease at diagnosis (ileal, colonic, ileocolonic, upper gastrointestinal tract); prior appendectomy; smoking status (current smoker [>1 cigarette/day] vs. never or ex-smoker); extraintestinal manifestations at diagnosis; perianal disease at diagnosis; and steroids required for the treatment of the first flare. Variables with a $p$ value below 0.1 in the univariate analysis were further included in a logistic multivariate regression analysis, and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Those variables with >15% of missing values were rejected. A $p$ value <0.05 was considered statistically significant. Kaplan-Meier survival curves were plotted to analyze the relationship between the follow-up time and the development of disabling CD. Patients were excluded from the Kaplan-Meier analyses if they had missing values for date of diagnosis of disabling disease.

To create a practical tool to estimate the risk of developing disabling disease in a subgroup of patients with noncomplicated CD at diagnosis, a prognostic nomogram integrating all significant predictive factors from our multivariable logistic regression analysis was generated. The internal validation of the nomogram was performed using 1,000 bootstrap resampling. The discrimination of the nomogram was evaluated calculating the area under the receiver operating characteristic curve (AUC), with 95% CI and the associated $p$ value representing the likelihood of the null hypothesis (AUC = 0.5). The statistical analyses were performed using R (V4) and rms (v6 2-0) package.

## Results

The patients' medical records of five hundred and sixty-eight patients were initially reviewed and 57 of them were excluded because of incomplete data. Thus, a total of 511 patients with CD were included in the study. Distribution of the patients' characteristics at diagnosis is presented in Table 1. Among the 511 patients, 268 (52.4%) were females. Steroids were required for treating the first flare-up in 330 (64.6%) patients. Perianal lesions were present at diagnosis in 94 (18.4%) patients and extraintestinal manifestations in 75 (14.7%). Most patients (381, 74.6%) developed disabling disease within 5 years after diagnosis. The median time to develop disabling CD was 29.3 months (95% CI = 24.8–34.8), with

**Table 1.** Distribution of patients' characteristics at diagnosis according to the non-disabling or disabling clinical course of the disease in the 5-year period after diagnosis

| Variables | All cases ($n$ = 511), $n$ (%) | Non-disabling ($n$ = 130), $n$ (%) | Disabling ($n$ = 381), $n$ (%) | $p$ value |
|---|---|---|---|---|
| Male gender | 243 (47.5) | 46 (35.4) | 197 (51.7) | 0.001 |
| Age at onset <40 years | 442 (86.5) | 103 (79.2) | 339 (89.0) | 0.005 |
| Location of the disease | | | | 0.001 |
| L1: ileal | 212 (41.5) | 60 (46.2) | 151 (39.9) | |
| L2: colonic | 110 (21.5) | 39 (30) | 71 (18.6) | |
| L3: ileocolonic | 164 (32.1) | 29 (22.3) | 136 (35.4) | |
| L4: upper | 25 (5.0) | 312 (1.6) | 23 (6.1) | |
| Extensive disease (L3/L4) | 189 (36.9) | 31 (23.8) | 158 (41.5) | |
| Behavior of the disease | | | | 0.080 |
| B1: inflammatory | 375 (73.4) | 105 (80.8) | 270 (70.9) | |
| B2: stricturing | 75 (14.7) | 16 (12.3) | 59 (15.5) | |
| B3: penetrating | 61 (11.9) | 9 (6.9) | 52 (13.6) | |
| Previous appendectomy | 38 (7.4) | 6 (4.6) | 32 (8.4) | 0.340 |
| Smoking at diagnosis | 218 (42.7) | 48 (36.9) | 170 (44.6) | 0.060 |
| Requirement of steroids | 330 (64.6) | 67 (51.5) | 263 (69.0) | 0.001 |
| Perianal lesions at diagnosis | 94 (18.4) | 14 (10.8) | 80 (21.0) | 0.005 |
| Extraintestinal manifestations | 75 (14.7) | 16 (12.3) | 59 (15.5) | 0.500 |

a cumulative probability for developing disabling CD of 27.9%, 44.5%, and 72.5% at 1, 3, and 5 years after diagnosis, respectively (shown in Fig. 1).

Search for factors available at diagnosis predictive of disabling CD course during the 5-year period following diagnosis was performed in all patients. Results of the univariate analysis are presented in Table 1, showing that development of disabling CD was associated with gender, age at onset, location of the disease, requirement of steroids for the first flare, and presence of perianal disease at diagnosis.

In the multivariate analysis (Table 2), male gender (OR = 1.98, 95% CI = 1.26–3.11; $p$ = 0.003), age at onset less than 40 years (OR = 1.82, 95% CI = 1.0–3.32; $p$ = 0.050), ileal or colonic location of the disease at diagnosis (OR = 0.45, 95% CI = 0.27–0.74; $p$ = 0.002), the need for steroids at the first flare (OR = 2.43, 95% CI = 1.54–3.84; $p$ = 0.001), and perianal lesions at diagnosis (OR = 2.01, 95% CI = 1.06–4.14; $p$ = 0.03) were independently associated with the development of disabling disease.

We also developed a model for the prediction of disabling CD in a subgroup of patients with purely non-stricturing non-fistulizing disease at diagnosis and without perianal disease (310 out of 511 patients, 60.7%). Clinical, demographic, and biological parameters according to the non-disabling (62 patients) or disabling clinical course of the disease (248 patients, 80%) in these patients are shown in Table 3. Of the 310 patients, 135 (43.1%) were males, with a median age at diagnosis of 28.5 years (standard deviation = 12.3; range = 5.4–76.3 years). CD initially involved ileum, colon, ileum and colon, or only small bowel in 121 (39%), 79 (25.5%), 100 (32.3%), and 10 (3.2%) of patients, respectively. Steroids were required for treating the first flare-up in 213 (68.7%) patients. Among the 310 patients, 23 (7.4%) had a previous history of appendectomy, 28 (9.0%) had familiar history of IBD, and 136 (43.9%) were smokers. The symptoms present at diagnosis were fever in 58 (18.7%) and extraintestinal manifestations in 45 (14.5%) patients. In the univariate analysis (Table 3), male gender, age at onset <40 years, location at diagnosis, and requirement of steroids for the first flare were associated with the development of a severe CD. Regarding laboratory findings, albumin levels were associated with the development of a disabling CD.

Clinical, demographic, and biological variables that had $p$ values <0.1 in the univariate analysis (all parameters except previous appendectomy, fever, extraintestinal manifestations, family history of IBD, hemoglobin, and CRP) were entered into the multivariate analysis. In the multivariate analysis, age at onset less than 40 years (OR = 3.46, 95% CI = 1.52–7.90; $p$ = 0.03), extensive disease (L3/L4) (OR = 2.67, 95% CI = 1.18–6.06; $p$ = 0.02), smoking habit (OR = 2.09, 95% CI = 1.03–4.27; $p$ = 0.04), requirement of steroids at the first flare (OR = 2.20, 95% CI = 1.09–4.45; $p$ = 0.03), and albumin (OR = 0.59, 95% CI = 0.36–0.96; $p$ = 0.03) were independently associated with the development of disabling disease (Table 4).

The Kaplan-Meier curve of development of disabling CD in the subgroup of 310 patients with purely non-stricturing non-fistulizing disease at diagnosis is

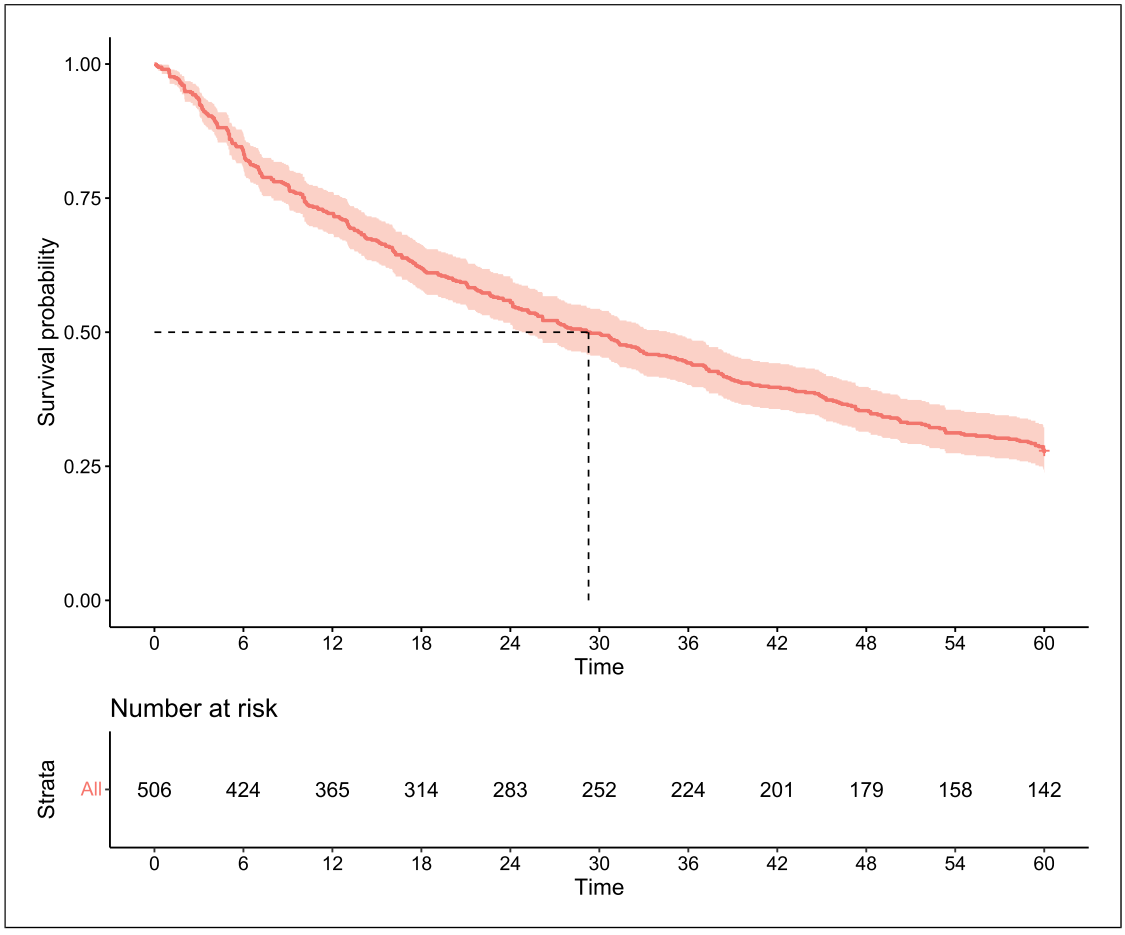


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**Fig. 1.** Kaplan-Meier survival curve depicting the development of disabling Crohn's disease over time in Crohn's disease patients with a minimum follow-up of 5 years after diagnosis. $N = 506$ due to missing values. Time on the $X$-axis is represented in months.

**Table 2.** Multivariate analysis of baseline factors according to the development of disabling clinical course in the 5-year period after diagnosis

| Variables | Hazard ratio | 95% CI | *p* value |
|---|---|---|---|
| Male gender | 1.98 | 1.26–3.11 | 0.003 |
| Age at onset <40 years | 1.82 | 1.00–3.32 | 0.050 |
| Extensive disease (L3/L4) | 2.33 | 1.36–3.67 | 0.002 |
| Inflammatory behavior of the disease (B1) | 0.61 | 0.35–1.06 | 0.080 |
| Smoking at diagnosis | 1.24 | 0.79–1.96 | 0.340 |
| Requirement of steroids at the first flare | 2.43 | 1.54–3.84 | 0.001 |
| Perianal lesions at diagnosis | 2.10 | 1.06–4.14 | 0.030 |

presented in Figure 2. The curve shows that the median time to develop disabling CD in this subset of patients was 35.8 months (95% CI = 30.6–44.8).

A nomogram was constructed based on the multivariable logistic regression model, in order to predict the risk of developing disabling disease (Fig. 3). Each predictor variable (age at diagnosis <40 years, extensive disease, smoking at diagnosis, need for steroids at the first flare, and albumin levels) has a corresponding point value based on its contribution to the model. To calculate the probability of developing disabling CD, the value of each risk factor is obtained by drawing a vertical line straight

**Table 3.** Distribution of clinical, demographic, and biological parameters according to the non-disabling or disabling clinical course of the disease in the 310 patients with purely non-stricturing non-fistulizing Crohn's disease at diagnosis without perianal disease (SD: standard deviation)

| Clinical and demographic variables | Non-disabling ($n$ = 62), $n$ (%) | Disabling ($n$ = 248), $n$ (%) | $p$ value |
|---|---|---|---|
| Male gender | 18 (29.0) | 116 (46.8) | 0.010 |
| Age at onset <40 years | 45 (72.6) | 222 (89.5) | 0.002 |
| Extensive disease (L3/L4) | 12 (19.3) | 99 (39.9) | 0.003 |
| Previous appendectomy | 2 (3.2) | 21 (8.5) | 0.320 |
| Smoking at diagnosis | 22 (35.5) | 121 (48.8) | 0.060 |
| Requirement of steroids at the first flare | 31 (50.0) | 180 (72.6) | 0.001 |
| Fever (T >38°C) | 7 (11.3) | 51 (20.6) | 0.128 |
| Extraintestinal manifestations | 7 (11.3) | 37 (14.9) | 0.670 |
| Family history of IBD | 3 (4.8) | 25 (10.1) | 0.130 |
| **Biological parameters** | **Non-disabling ($n$ = 62), mean (SD)** | **Disabling ($n$ = 248), mean (SD)** | **$p$ value** |
| Hemoglobin, g/dL | 12.5 (2.0) | 12.2 (2.0) | 0.350 |
| C-reactive protein, mg/dL | 26.71 (43.0) | 33.94 (44.8) | 0.270 |
| Albumin, g/dL | 3.8 (0.6) | 3.5 (0.7) | 0.030 |

upward from that variable to the "Points" scale. Then, the points for each variable are summed and located on the "Total Points" scale of the nomogram. Finally, a vertical line is drawn from the total points axis to the "Risk of Disabling" scale to obtain the probability of developing disabling disease. The term "Linear Predictor" is a coordinate axis of the linear predicted value (a linear function of a set of coefficients and explanatory variables), whose value is used to predict the outcome of a variable. This value is converted to the corresponding probability value by a certain transformation function [31]. After bootstrapping for internal validation, the bootstrap-corrected AUC of the prediction model was 0.723 (95% CI = 0.670–0.830) with 1,000 resamplings, indicating that the established nomogram had good discrimination in predicting disabling CD.

## Discussion

CD is a chronic disease that has a progressive and destructive course, although clinical presentation at diagnosis and the disease course is heterogeneous and variable over time. The majority of patients have uncomplicated disease at diagnosis, but most eventually develop complications. Thus, it is crucial to identify factors predicting a severe course of the disease at diagnosis to optimize a personalized therapeutic approach that could alter the natural history of CD.

In our research, we initially identified the need for steroids at the first flare, the presence of perianal lesions, and young age at diagnosis (<40 years) as significant independent factors associated with the development of disabling disease in a large cohort of patients, during the first 5 years after initial diagnosis. The results obtained are in agreement with previous studies in the field [10, 16, 20]. We additionally found that male gender and ileal or colonic location of the disease were also predictors of disabling disease. So far, male gender has not been reported to be correlated with the further development of severe disease, although it has been described as a bad prognosis factor in some clinical scenarios [32]. According to disease location, ileocolonic location (L3) – with or without concomitant upper gastrointestinal disease (L4) – was associated with a significantly increased risk for progression of the disease as compared to an isolated ileal or colonic location. These findings are also in line with two previous works [16, 20] and represent an important step forward in the identification of new clinical parameters that could help clinicians establish appropriate therapeutic strategies at diagnosis. Nonetheless, the predictive model for the development of disabling CD described by Beaugerie et al. [16] is not useful enough to guide clinical practice nowadays. One of the reasons for this is the inclusion of perianal disease as a risk factor since the management of perianal disease requires an early treatment with biologics and a multidisciplinary approach to minimize complications [33]. On the other side, the model

**Table 4.** Multivariate analysis of baseline prognostic factors according to the development of disabling clinical disease during the entire course of the disease in non-stricturing, non-fistulizing Crohn's disease at diagnosis

| Variables | Odds ratio | 95% CI | *p* value |
|---|---|---|---|
| Male gender | 1.95 | 0.94–4.05 | 0.070 |
| Age at onset <40 years (A1-A2) | 3.46 | 1.52–7.90 | 0.030 |
| Extensive disease (L3/L4) | 2.67 | 1.18–6.06 | 0.020 |
| Smoking at diagnosis | 2.09 | 1.03–4.27 | 0.040 |
| Requirement of steroids at the first flare | 2.20 | 1.09–4.45 | 0.030 |
| Albumin | 0.59 | 0.36–0.96 | 0.030 |

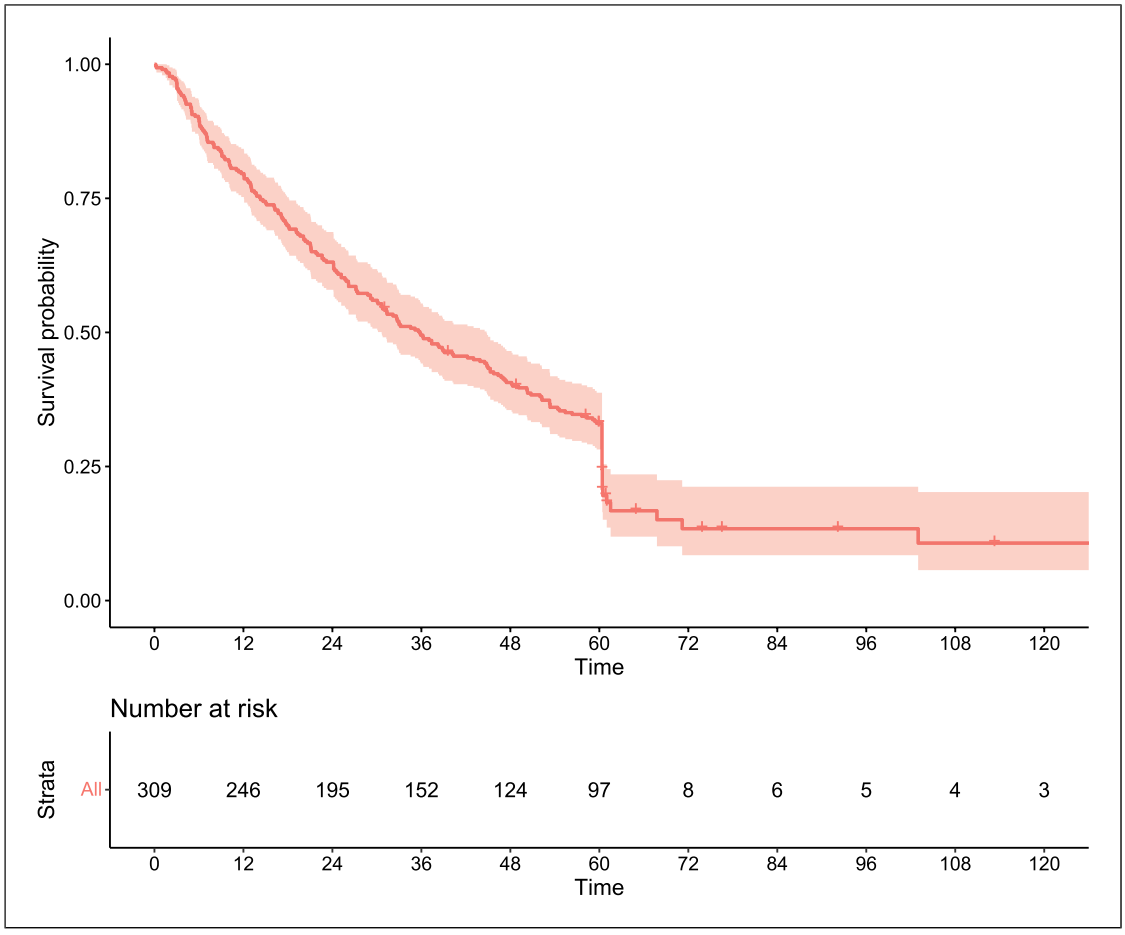


**Fig. 2.** Kaplan-Meier survival curve depicting the development of disabling Crohn's disease during the entire course of the disease in non-stricturing, non-fistulizing disease at diagnosis. $N = 309$ due to missing values. Time on the $X$-axis is represented in months.

does not differentiate between patients who have more aggressive phenotypes, fistulizing or structuring, to those with potentially more benign CD course. The former are candidates for surgical or biological therapy from the beginning [34, 35], and therefore their inclusion in the prognostic model provides an inaccurate prediction of negative outcomes in the later patients.

In fact, in the past 2 decades, the emergence of biological therapies and new treatment paradigms has revolutionized the medical management of CD. The early combined immunosuppression in high-risk patients has been demonstrated to promote mucosal healing, minimize exposure to corticosteroids and reduce the need for surgery [36–38]. This "top-down" approach suggests that

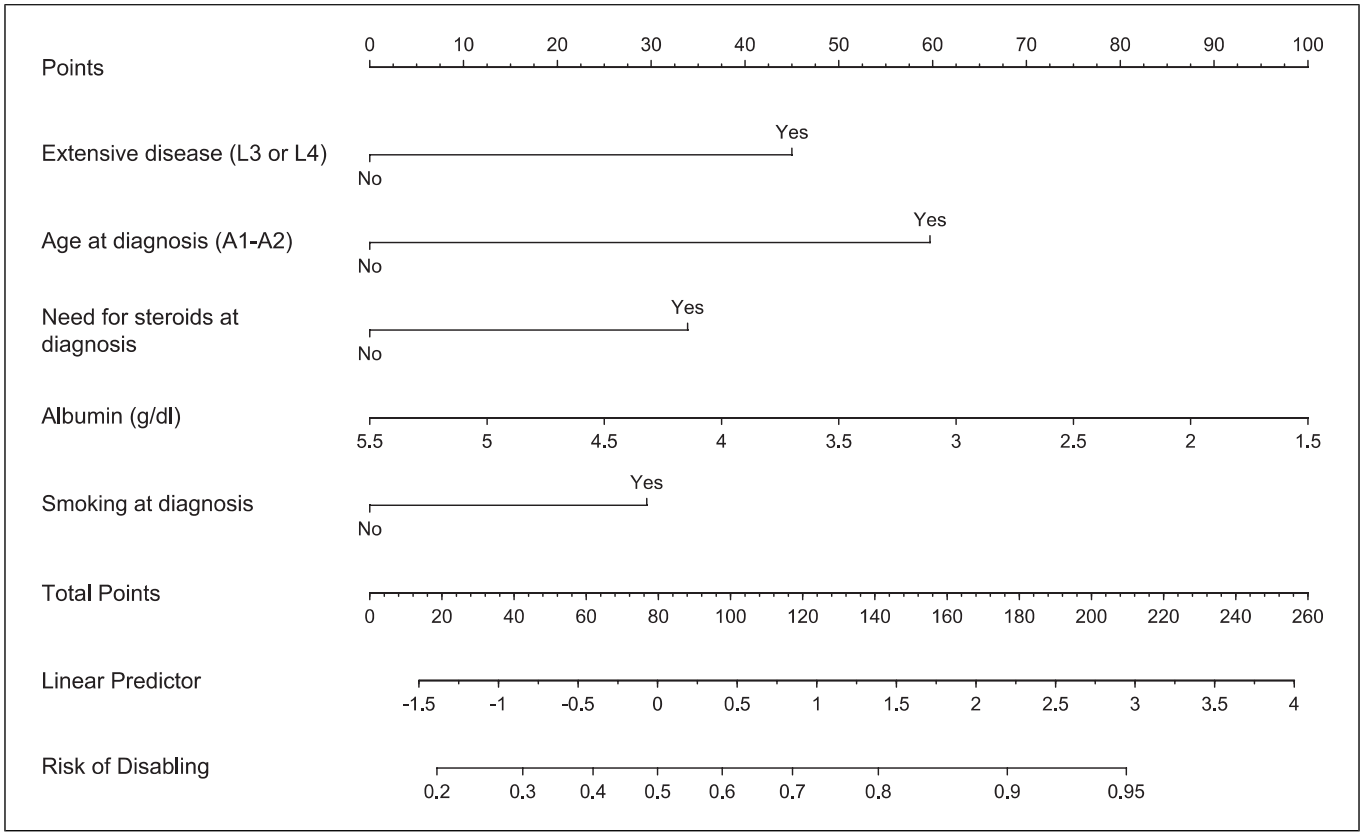


**Fig. 3.** A prognostic nomogram for risk of developing disabling Crohn's disease (CD) during the entire course of the disease in patients with Crohn's disease. The nomogram consists of 5 significant risk factors. Each factor was associated with the number of points. To calculate the probability of developing disabling CD, the value of each predictor is obtained by drawing a vertical line straight upward from that factor to the points' axis, then summed the points achieved for each predictor and located this sum on the total points' axis of the nomogram, where the probability of developing disabling disease can be located by drawing a vertical line downward.

a prompt introduction of such therapies might prevent a disabling disease course. Nonetheless, there is mounting evidence on both benefits and disadvantages in the application of this therapy, and the choice of either top-down or a more traditional step-up strategy in the treatment of CD should be based on an individualized approach [14, 39]. Therefore, accurate identification of those patients at higher risk for rapid disease progression is of great value in stratifying patients at the time of diagnosis into a more or less aggressive treatment paradigm. This would reduce the disadvantages related to any of the strategies, minimizing toxicity and leading to more efficient use of resources [18, 40].

Consequently, in the second part of our study, we developed a model for the prediction of disabling CD in a subgroup of patients with purely non-stricturing non-fistulizing disease at diagnosis and without perianal disease. Moreover, we considered other potential clinical and biological risk factors and increased the follow-up period to the entire course of the disease. In this subgroup of patients (310 out of 511 patients), young age at diagnosis (<40 years), extensive disease, smoking habit, the need for steroids at the first flare, and albumin levels were also independently associated with an unfavorable outcome of the disease.

Among the laboratory variables analyzed, albumin was the only parameter that could be associated with a negative evolution of the disease. It has been described that low serum levels of albumin are a result of various conditions, including a reduced nutrition status or a systemic inflammatory response. In addition, low albumin concentration has been suggested to be a potential marker for assessing disease activity in patients with CD [41]. These results indicate that serum albumin levels may be considered predictive of progression toward complicated disease.

We also developed and internally validated a nomogram model to predict the risk of developing disabling CD in patients with noncomplicated disease at diagnosis. This visual, user-friendly, and intuitive prognostic device has been widely used as a tool in the diagnosis, treatment, and prognosis of various diseases, including CD [42–44]. Our nomogram consisted of 5 independent risk factors (age at onset <40 years, extensive disease, smoking at diagnosis, need for steroids at the first flare, and albumin), which are easily obtainable during patients' admission to the hospital. The results suggested a good prognostic discrimination ability of the nomogram. Therefore, this clinical prediction model could be used as a rapid scoring system in the clinical setting to help identify patients at risk to develop aggressive CD and to approach their treatment more effectively. More importantly, tailored therapy with more aggressive treatment in high-risk patients might enhance their quality of life or even influence the natural course of CD. At the same time, the nomogram could also be used as a clinical prediction tool for detecting patients with a low risk of developing disabling CD, who can be treated with more conventional management.

In our study, the vast majority of the study population (80%) was classified as having a disabling disease course probably reflecting that the majority of patients were selected from tertiary centers. The high rates of prevalence of disabling CD observed in our work are similar to those reported in previous published studies. For instance, in the original study of Beaugerie et al. [16], the estimated prevalence of disabling disease was around 64.9%–80.5%, depending on how the loss to follow-up patients was handled. In the study conducted by Loly et al. [20], also using the same definition of disabling CD, this percentage was lower (close to 60%). Yang et al. [10], who used a similar definition of disabling CD – the presence of chronic symptoms like diarrhea, fever, fatigue was not considered – describe a rate of disabling disease of 80.2% at 5 years after diagnosis in a Chinese population of patients with IBD.

According to these results, a considerable percentage of patients will develop a disabling disease and could profit from a top-down strategy, although this percentage might be considered too high for an optimal benefit-risk ratio. Nonetheless, although there is controversy in the medical community over the safety, efficacy, and cost involved with top-down therapy, this strategy is proved to be a cost-effective treatment given current data [14].

Our study was conducted on a robust population-based sample of patients who were representative of several regions of Spain. However, the analysis is subject to several limitations. The first limitation of this study is its retrospective design, being subject to inherent bias, although we strengthened our work by including a long follow-up period. Second, although we performed an internal resampling validation on the established nomogram to estimate the generalizability of the model, an external validation with data available from a different population, setting, or time period would reinforce the reliability of our model. Nevertheless, although the conclusions of this study need to be confirmed in prospective studies, our research findings may have a certain degree of generality because of the high number of centers involved in the study.


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## Statement of Ethics

Each participating center retrieved data from the ENEIDA database [28]. All patients included in the database signed an informed consent document authorizing the use of their clinical data for research purposes. The use of the ENEIDA database was approved by the Ethics Committee of each participating center in 2006.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

G.B., M.A., and P.N. conceived and designed the study. G.B., O.M., M.A., M.B., Y.Z., D.G., D.C., F.M., D.M., I.C., V.G., C.L., A.L., J.M.H., C.C., X.A., and A.P. were responsible for patient inclusion and data collection. G.B. was responsible for data managing and constructing the centralized database. G.B. and M.A. performed the statistical analysis. G.B. wrote the first draft of the paper. G.B., M.B., M.A., E.D., and P.N. reviewed and edited the final manuscript. All authors reviewed and approved the final version.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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