Crohn's Disease in a Southern European Country: Montreal Classification and Clinical Activity

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Background: Given the heterogeneous nature of Crohn's disease (CD), our aim was to apply the Montreal Classification to a large cohort of Portuguese patients with CD in order to identify potential predictive regarding the need for medical and/or surgical treatment.

Methods: A cross-sectional study was used based on data from an on-line registry of patients with CD.

Results: Of the 1692 patients with 5 or more years of disease, 747 (44%) were male and 945 (56%) female. On multivariate analysis the A2 group was an independent risk factor of the need for steroids (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.1–2.3) and the A1 and A2 groups for immunosuppressants (OR 2.2; CI 1.2–3.8; OR 1.4; CI 1.0–2.0, respectively). An $L3+L3_4$ and L_4 location were risk factors for immunosuppression (OR 1.9; CI 1.5–2.4), whereas an L1 location was significantly associated with the need for abdominal surgery ($P < 0.001$). After 20 years of disease, less than 10% of patients persisted without steroids, immunosuppression, or surgery. The Montreal Classification allowed us to identify different groups of disease severity: A1 were more immunosuppressed without surgery, most of A2 patients were submitted to surgery, and 52% of $L1+L1_4$ patients were operated without immunosuppressants.

Conclusions: Stratifying patients according to the Montreal Classification may prove useful in identifying different phenotypes with different therapies and severity. Most of our patients have severe disease.

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Key Words: Crohn's disease, Montreal Classification, Portugal, southern Europe, predictive factors, clinical activity

Crohn's disease (CD) is a chronic inflammatory disease associated with significant morbidity due to a frequent need for intestinal resections and hospitalizations. Accurate classification of CD would be most helpful in this respect to allow an early assessment of disease prognosis, thereby identifying and selecting patients for the most appropriate therapy according to disease subtype. The Montreal[1] revision of the Vienna Classification, to our knowledge, was never validated in a large population cohort.

Furthermore, geographic variations in CD incidence and prevalence have long been reported, with Scandinavian countries exhibiting a higher incidence, as well as a more aggressive behavior as compared to patients from southern Europe.[2] However, this assumption might be difficult to substantiate because, so far, very few population-based studies from southern Europe have been published. Also, most studies reporting on the natural history of CD utilized referral

centers, which may create a "referral center" bias, that is, patients referred to quaternary medical centers may have the most severe phenotypes, most likely to undergo surgery and multiple medications, and may well not be a representative sample.

The purpose of the present study was to apply the Montreal Classification in a large cohort of Portuguese patients with CD from several centers across the country in order to minimize "referral bias" and then search for predictive factors that would enable us to identify patients requiring steroid treatment, immunosuppression, and/or abdominal surgery. The Montreal Classification was used to allow a uniform and standardized classification of the cohort, thereby making possible for us to understand the clinical activity of this group of patients in a southern European country.

PATIENTS AND METHODS

Patient Inclusion

From September 2004 until December 2006, all medical doctors in Portugal (gastroenterologists, pediatricians, surgeons, and general practioners) were invited to include patients with IBD in a national database registry. Our national database was approved by national authorities and was implemented by the Portuguese group of studies for IBD (http://www.gedi.med.up.pt/). It is a cross-sectional study that includes 77 Portuguese MDs coming from 33 medical centers, distributed all over Portugal, from north to south, including the islands of Madeira and Azores. Patient registration was carried out through a Web-based system with password and user name validated by a scientific committee. The patients came from quaternary and tertiary referral hospitals (48.6%) and regional hospitals plus private practice (50.7%). A small percentage (0.5%) was included by pediatricians working in referral pediatric centers. These figures represent about 50% of the calculated number of Portuguese patients with IBD. All definitions of the material form were online and all participants had at least 3 meetings per year to discuss the inclusion criteria. All patients included in the present study had to fulfill the strict international diagnostic criteria for IBD.[3] In addition, all patients were required to have at least 2 criteria from the *Copenhagen Diagnostic Criteria of CD*.[3]

Data Collection

Information on date of onset of symptoms and diagnosis, type of clinical onset, extent of disease, familial occurrence of IBD, presence of extraintestinal manifestations, type of colonic involvement, presence of rectal involvement, type of anal lesion, previous history of abdominal abscesses and/or fistulas, clinical course, response to steroids, immunosuppression and/or biologic treatment, as well as previous abdominal or anal surgery was collected. Abdominal surgery was considered as such when patients submitted to surgery for intes-

tinal resection, abscess drainage, strituroplasty, or another procedure such as appendectomy or acute abdomen without intestinal resection (i.e., diagnosis of CD without resection). The Montreal Classification[1] was used. In this classification, L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal (GI) disease is present. Behavior was defined as B1 nonstricturing, nonpenetrating, B2 stricturing, B3 penetrating, and p is added to B1–B3 when concomitant perianal disease is present. Patients were defined as steroid-dependent if it was not possible to decrease the prednisolone dose below 10 mg/day or if they required 2 or more steroid treatments (1 mg/kg) within a period of 6 months. Steroid resistance was defined as an incapability of inducing remission with steroids at a dose of 1 mg/kg. Patients who have had treatment with azathioprine, 6-MP, cyclosporine, or methotrexate were included in the immunosuppression group.

Disease Severity

Patients were classified in 6 disease severity categories, a modification of the Silverstein et al[4] classification. Score 1 was reserved for mild disease (without steroids, immunosuppressants, biologic treatment, or surgery at any given year of disease); score 2 for moderate disease (patients treated with corticosteroids requiring a dose of prednisolone above 10 mg/day or 2 or more steroid treatments within a period of 6 months); score 3 for severe disease (patients treated with immunosuppressants without biologic treatment or surgery); score 4 for severe refractory disease (patients treated with immunosuppressants and biologic treatment without surgery); score 5 for surgically treated disease (patients without use of immunosuppressants or biologic treatment); and finally, score 6 for severe refractory disease who came to need surgery and also immunosuppressants and biologic treatment.

Statistics

The Kolmogorov–Smirnov test was used to test for normality. When testing a hypothesis about continuous variables, parametric tests (Student's *t*-test and 1-factor analysis of variance, ANOVA) and nonparametric tests (Mann–Whitney and Kruskal–Wallis tests) were used as appropriate, taking into account normality assumptions and the number of groups compared. When testing a hypothesis about categorical variables a chi-square test and Fisher's exact test were used, as appropriate. In order to have a more thorough understanding of the factors associated with the use of steroid therapy, immunosuppression and abdominal surgery univariate and multivariate logistic regression modeling was used. In the multivariate logistic regression models the dependent variables were steroid therapy, immunosuppression, and abdominal surgery. Model goodness-of-fit was assessed using the Hosmer–Lemeshow statistic and discriminative power was evaluated by receiver-operator curve (ROC) curve analysis. The influence of outlier data values on model fit was
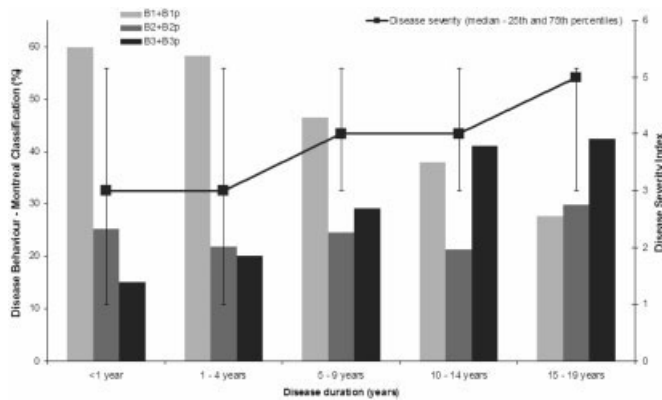
FIGURE 1. Behavior categories according to the Montreal Classification and clinical activity in different intervals of disease duration. Relative frequency (percentage) for each disease behavior category: Montreal Classification (left axis) and disease severity index (right axis) classified in 6 disease severity categories according to the modified Silverstein et al[4] classification for each of the disease duration groups: <1 year ($n = 274$); 1–4 years ($n = 761$); 5–9 years ($n = 673$); 10–14 years ($n = 354$); and 15–19 years ($n = 191$).

estimated using leverage statistics, and collinearity was assessed by evaluation of coefficients correlation matrix. Because of the multiple hypothesis tests performed and presented in this study, the inflation of type I error is a risk. Whenever statistical hypothesis testing is used and in order to take into account a correction for the multiple comparisons presented, using the Bonferroni method, the significance level should be adequately corrected to $\alpha = 0.002$ instead of the traditional $\alpha = 0.05$ level. Statistical analysis was performed using the software Statistical Package for the Social Sciences v. 15.0 for Windows (SPSS, Chicago, IL).

RESULTS

Analysis of Montreal Categories

Of the 2854 patients with CD in our database, 1245 (44%) were male and 1609 (56%) female, with a mean age at

diagnosis of 32 ± 14 years and a median time after diagnosis of 6 years (percentile 25, 2 and percentile 75, 11). Only patients with 5 or more years of disease were included in this analysis because it is a necessary timepoint before behavior might be classified. This approach seems to be imperative when results of different centers are compared. Behavior progression and clinical severity at different intervals of disease duration are shown in Figure 1. Sixty percent of patients in the first year of disease were categorized as B1; moreover, this percentage decreases with disease progression and only 28% of those with 15–19 years of disease had no stenosing or penetrating event (B1). By contrast, the B3 group increases in those with longer disease duration, achieving 42% in the longest affected group. Considering disease severity, we observed that during the first 4 years of disease the median severity was 3 (interquartile range 1–5), increasing to 4 (3–5) in those with 10–14 years of disease, and to 5 (3–5) in patients with 15–19 years of disease duration.

Table 1 shows characteristics of our study group according to age of diagnosis. Of the 1692 patients, 747 (44%) were male and 945 (56%) female. Mean age at diagnosis was 31 ± 13 years. Median time after diagnosis was 10 years (percentile 25, 7 and percentile 75, 16). With regard to age at diagnosis, 8% were classified as A1 (below 16 years), 73% as A2 (below 40 years), and 19% as A3 (above 40 years). Median time of follow-up after diagnosis was 10 years (percentile 25%, 7; percentile 75%, 16). A family history of IBD was present in 8% of the patients.

Table 2 shows classification of patients according to the Montreal Classification. Appropriate allocation of patients to different categories of disease location, age of onset, and behavior was possible in 1413 patients: 34% were classified as L1 (ileal), 15% as L2 (colonic), 45% as L3 (ileocolonic), and 1% as L4 (upper GI disease). B1 (nonstricturing, nonpenetrating) phenotype was found in 38% of patients; B2 (structuring) in 26% and B3 (penetrating) in 36%. Colonic

TABLE 1. Baseline Population Characteristics

| | Age at Diagnosis | | | | |
	≤ 16 years N (%)	17–40 years N (%)	>40 years N (%)	$\Sigma\ N$ (%)	P^a
Gender					
Male	63 (45)	541 (44)	143 (45)	747 (44)	0.107
Female	77 (55)	691 (56)	177 (55)	945 (56)	
Age (mean ± SD)	13 ± 2	27 ± 6	52 ± 9	31 ± 13	
Years of disease[b]	10 (7–16)	10 (7–16)	9 (6–14)	10 (7–16)	0.003
Family history of IBD	8 (7)	77 (9)	14 (7)	99 (8)	0.546

[a]Continuous variables were compared by Kruskal-Wallis (variables where normal distribution could not be assumed) and by 1 factor analysis of variance (variables where normal distribution could be assumed) and for categorical variables the Pearson chi-square test was used.
[b]Median (percentile 25 –percentile 75) after diagnosis.

TABLE 2. Allocation of Patients to All 126 Subgroups of the Montreal Classification

	A1						A2						A3						
	B1	B2	B3	B1p	B2p	B3p	B1	B2	B3	B1p	B2p	B3p	B1	B2	B3	B1p	B2p	B3p	Σ
L1	0.8	0.5	0.4	0	0.3	0.1	6.4	9.1	6.7	0.2	0.6	1.7	2.4	2.3	1.8	0.1	0.1	0.4	33.8
L2	0.8	0.1	0.2	0	0.1	0.3	6.9	0.5	1.6	0.6	0.1	0.8	1.8	0.4	0.6	0.4	0	0.1	15.1
L3	1.4	0.8	1.1	0	0.1	0.6	9.8	7.5	10.3	0.7	0.6	4.3	2.8	1.6	2.0	0.1	0.1	0.7	44.7
L4	0	0	0	0	0	0	0.3	0.5	0.2	0	0	0	0.1	0.1	0	0	0	0	1.2
L1$_4$	0.2	0	0.1	0	0	0	0.8	0.6	0.8	0	0.1	0	0.3	0.3	0.2	0	0	0	3.3
L2$_4$	0	0.1	0.1	0	0	0	0.4	0.1	0.5	0	0	0.1	0.1	0.1	0.1	0	0	0	1.5
L3$_4$	0	0	0	0	0	0	0.1	0.1	0	0	0	0	0	0	0.1	0	0	0	0.4
Σ	3.3	1.5	1.9	0	0.5	1	24.7	18.3	20	1.6	1.3	6.9	7.6	4.7	4.8	0.6	0.2	1.2	100

Percentage of the total population ($n=1413$) is shown.

involvement was total in 23% patients, proximal in 30%, segmental in 32%, and left colonic involvement in 15%.

Analysis of Location, Behavior, and Treatment According to Age of Onset of CD

A significant association between the age at diagnosis and disease location was found, with the youngest population (A1) exhibiting predominantly L3 involvement, whereas the oldest patients (A3) had mainly an L2 location ($P < 0.001$). The A1 group of patients were more often steroid-dependent (36%, $P = 0.030$) and were more often taking immunosuppressants (62%, $P < 0.001$) and biologic agents (22%, $P < 0.001$) (Table 3). By contrast, we observed that the A3 group (>40 years at diagnosis) had a lower incidence of abdominal fistulas and both steroids and immunosuppressants were less often prescribed (Table 3).

Severity

The population was stratified by different years of disease duration. In all, 1704 patients had at least 5 years of disease, 919 patients 10 or more years, 497 at least 15 years, 262 20 or more years of disease, and 136 had disease for at least 25 years. It was observed that only a minority of patients ($<10\%$) did not receive steroids, immunosuppressants, or were submitted to abdominal surgery. Twenty-seven percent of patients became steroid-dependent and 49% of them required immunosuppressants, with or without biologic treatment. Of note, the majority of patients required surgery at some point—at 5 years of diagnosis the first surgery rate was 22% rising to 38.5%, 52%, 67%, and 66%, at 5–9, 10–14, 15–19, 20–24, and more than 25 years after diagnosis, respectively. Table 4 shows the severity of disease in 6 different categories according to the Silverstein et al[4] modified classification. Thus, considering age of onset it was observed that 20% patients in the A3 group were assessed as mild disease and only 7% were stratified in the highest severe

TABLE 3. Contingency Table for Age at Diagnosis, Type of Penetrating Events, Medical and Surgical Treatment

	A1 N (%)	A2 N (%)	A3 N (%)	P^a
Location				
L1+L1$_4$	66 (32)	733 (36)	226 (38)	
L2+L2$_4$	31 (15)	408 (20)	161 (27)	0.001
L3+L3$_4$	107 (52)	847 (42)	208 (35)	
L4	2 (1)	22 (1)	7 (1)	
Upper GI involvement				
	7 (5)	72 (6)	22 (7)	0.693
Behavior				
B1+B1p	86 (48)	788 (45)	273 (52)	
B2+B2p	45 (25)	444 (25)	123 (23)	0.047
B3+B3p	49 (27)	527 (30)	128 (24)	
EIM	61 (44)	429 (35)	110 (35)	0.07
Abdominal penetrating events				
Abscesses	24 (17)	176 (15)	38 (12)	0.298
Fistulas	21 (15)	231 (19)	39 (12)	0.018
Anal penetrating events				
Fissures	17 (12)	93 (8)	15 (5)	0.018
Abscesses	22 (16)	165 (13)	36 (11)	0.391
Fistulas	34 (23)	271 (22)	62 (19)	0.442
Patients treated				
with steroids	119 (88)	965 (82)	214 (72)	0.001
Steroid dependent	42 (36)	266 (28)	47 (22)	0.030
Steroid resistant	9 (8)	58 (6)	9 (4)	0.434
Immunosuppression	85 (62)	621 (51)	121 (38)	0.001
Biologic treatment	30 (22)	222 (18)	41 (13)	0.020
Abdominal surgery	64 (46)	609 (50)	141 (44)	0.215
Anal surgery	23 (17)	231 (19)	44 (14)	0.098

EIM, extraintestinal manifestations.
[a]Pearson chi-square test.

TABLE 4. Contingency for Age at Diagnosis, Location, and Behavior According to Treatment, Classified in 6 Disease Severity Categories (Modification of Silverstein et al[4] Classification) Silverstein Score

	Silverstein Score						
	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	P^a
Age onset							
A1	7 (8)	4 (5)	27 (32)	14 (17)	18 (21)	14 (17)	
A2	89 (12)	13 (2)	183 (24)	96 (13)	259 (35)	108 (14)	0.001
A3	41 (20)	5 (3)	38 (19)	24 (12)	80 (40)	14 (7)	
Location							
L1+L1$_4$	66 (18)	5 (1)	55 (15)	26 (7)	194 (52)	31 (8)	
L2+L2$_4$	32 (15)	7 (3)	70 (32)	59 (27)	26 (12)	25 (11)	0.001
L3+L3$_4$	36 (9)	8 (2)	120 (28)	49 (12)	135 (32)	76 (18)	
Behavior							
B1+B1p	100 (30)	11 (3)	13 (37)	48 (15)	38 (11)	14 (4)	
B2+B2p	15 (7)	2 (9)	33 (15)	4 (2)	146 (68)	16 (7)	0.001
B3+B3p	10 (3)	4 (1)	41 (14)	17 (6)	156 (52)	75 (25)	

Score 1 was reserved for mild disease (without steroids, immunosuppressants, biologic treatment or surgery at any given year of disease), score 2 for moderate disease (patients treated with corticosteroids requiring a dose of prednisolone above 10 mg/day or 2 or more steroid treatments within a period of 6 months), score 3 for severe disease (patients treated with immunosuppressants without biologic treatment or surgery), score 4 for severe refractory disease (patients treated with immunosuppressants and biologic treatment without surgery), score 5 for surgically treated disease (patients without immunosuppressants or biologic treatment), and score 6 to severe refractory disease who score 6 to severe refractory disease who came to need surgery and also immunosuppressants and biologic treatment. [a]Pearson chi-square test.

score. In contrast, the majority of A1 patients were treated with immunosuppressants without need of surgery and most of the A2 patients submitted to surgery (49%). When the patients were categorized by location it was possible to identify different groups of activity. It is very interesting that 52% of L1+L1$_4$ were operated on without immunosuppressants or biologic treatment. Regarding behavior classification, in the B1 group 30% of patients were classified as having mild disease, and in contrast 77% of penetrating patients required surgery.

Univariate and Multivariate Analysis of Factors Associated with Steroid Therapy, Immunosuppression, and Abdominal Surgery

Table 5 shows the variables that were associated with the use of steroids, immunosuppressants, and/or surgery on uni- and multivariate analysis. Of interest, early age of disease onset did not represent a risk factor for steroid dependency or abdominal surgery; however, the presence of extraintestinal manifestations (EIMs) was associated with increased risk of steroid dependence. With respect to immunosuppressants, we observed that besides the A1 and A2 groups, other risk factors were L3+L3$_4$ and L4 location, B2+B2p and B3+B3p groups, and the presence of perianal disease, EIM, as well as the previous use of steroids, namely, steroid dependency (odds ratio [OR] 10.3; 95% confidence interval [CI] 7.1–15.0) or steroid resistance (OR 6.7; CI 2.8–16.0). With regard to surgery, multivariate analysis

showed that risk factors were L1+L1$_4$ location, B2+B2p and B3+B3p behaviors, the presence of abdominal abscesses or fistulas, and steroid resistance.

DISCUSSION

Based on mesalamine consumption in the year 2005 and considering a daily drug intake-defined dose (DDD) of 2 g/day, the prevalence of IBD in Portugal was estimated to be 118 per 100,000 inhabitants, that is, 12,508 estimated Portuguese patients with IBD. The same study estimated a prevalence of CD of 60 per 100,000 inhabitants.[5] Based on these numbers, we believe that half of the CD patients in Portugal were included in this study, which may be considered a representative sample.

To our knowledge this is the first study assessing the Montreal Classification in a large cohort of patients with CD. Most of the patients came from hospitals from north to south Portugal, as well as the islands of Madeira and Azores, covering all types of hospital care (primary to quaternary) in an attempt to overcome a "referral-bias" which might have existed if we only included patients from major referral centers. Most of the investigators involved in the study were senior gastroenterologists, and patients seen in private practice were also included. The Montreal Classification individualized, for the first time, a group for early onset of disease, younger than 16 years old, allowing the investigation and categorization of a pediatric group. According to previous work, this group seems to be characterized by specific sero-

TABLE 5. Univariate and Multivariate Logistic Regression Models for Factors Associated with Steroid Treatment, Immunosuppression, and Abdominal Surgery

	N	Steroid Dependency Univariate Analysis OR (95% CI)	Steroid Dependency Multivariate Analysis[a] OR (95% CI)	Immunosuppression Univariate Analysis OR (95% CI)	Immunosuppression Multivariate Analysis[a] OR (95% CI)	Abdominal surgery Univariate Analysis OR (95% CI)	Abdominal surgery Multivariate Analysis[a] OR (95% CI)
Gender							
Male*	685	—	—	—	—	—	—
Female	869	1.251 (0.992–1.578)	1.227 (0.933–1.614)	0.912 (0.753–1.106)	0.845 (0.643–1.108)	1.092 (0.731–1.630)	−1.127 (0.829–1.532)
A1	134	2.062 (1.295–3.284)	1.739 (0.998–3.030)	2.611 (1.731–3.938)	2.209 (1.274–3.830)	1.092 (0.7301–1.630)	1.039 (0.562–1.920)
A2	1123	1.482 (1.073–2.047)	1.631 (1.119–2.377)	1.679 (1.301–2.162)	1.425 (1.006–2.019)	1.238 (0.966–1.586)	0.960 (0.650–1.419)
A3*	611	—	—	—	—	—	—
Years							
5–9*	714	—	—	—	—	—	—
10–14	389	0.963 (0.725–1.279)	0.969 (0.699–1.342)	1.117 (0.881–1.416)	0.923 (0.663–1.283)	1.603 (1.262–2.037)	1.676 (1.156–2.430)
15–19	209	0.996 (0.701–1.417)	1.251 (0.818–1.913)	1.009 (0.753–1.351)	0.783 (0.512–1.196)	2.004 (1.492–2.691)	1.996 (1.248–3.194)
20–24	116	1.186 (0.769–1.829)	1.042 (0.603–1.801)	1.208 (0.828–1.763)	0.748 (0.422–1.323)	3.957 (2.616–5.9214)	3.348 (1.687–6.642)
$L1+L1_4$*	521	—	—	—	—	—	—
$L2+L2_4$	306	1.669 (1.213–2.298)	1.339 (0.896–1.999)	1.875 (1.426–2.466)	1.406 (0.922–2.144)	0.208 (0.153–0.383)	0.226 (0.135–0.377)
$L3+L3_4$	691	1.267 (0.968–1.659)	1.163 (0.904–1.497)	2.124 (1.701–2.651)	2.165 (1.605–2.921)	0.762 (0.612–0.948)	0.575 (0.411–0.803)
L4	18	1.043 (0.357–3.232)	0.840 (0.232–3.039)	4.266 (1.501–12.130)	5.956 (1.865–19.026)	0.711 (0.278–1.816)	0.690 (0.202–2.353)
B1+B1p*	487	—	—	—	—	—	—
B2+B2p	341	0.622 (0.443–0.874)	0.719 (0.493–1.048)	1.135 (0.866–1.486)	1.666 (1.161–2.390)	16.261 (11.626–22.744)	12.732 (8.659–18.919)
B3+B3p	470	0.973 (0.730–1.298)	1.028 (0.657–1.608)	2.472 (1.928–3.168)	1.785 (1.138–2.800)	26.228 (18.838–35.516)	10.660 (6.533–17.393)
E.I.M*							
Present	565	1.949 (1.544–2.461)	1.758 (1.338–2.309)	1.833 (1.498–2.698)	1.543 (1.162–2.049)	0.902 (0.739–1.100)	0.876 (0.634–1.209)
Ab. abcesses*							
Present	221	1.064 (0.769–1.472)	0.978 (0.634–1.508)	2.029 (1.526–2.619)	1.361 (0.874–2.121)	10.649 (7·081–16.016)	3.668 (2.150–6.258)
Ab. fistula*							
Present	268	1.111 (0.825–1.498)	1.104 (0.711–1.715)	2.321 (1.778–3.029)	1.517 (0.974–2.363)	8.156 (5.833–11.405)	2.007 (1.2813–3.223)
Anal disease*							
Present	404	1.136 (0.878–1.468)	0.839 (0.552–1.274)	3.628 (2.852–4.615)	2.345 (1.539–3.573)	1.021 (0.820.–1.272)	0.804 (0.497–1.302)
Steroid[b]							
Dependence				8.597 (6.328–11.681)	10.386 (7.187–15.008)	0.993 (0.789–1.249)	1.031 (0.695–1.527)
Resistance				7.466 (3.693–15.095)	6.786 (2.866–16.063)	3.478 (2.051–5.899)	8.711 (3.651–20.784)
Immunosuppression[b]							
Ever used						1.510 (1.246–1.830)	1.333 (0.948–1.875)

OR, odds ratio; 95% CI, 95% confidence interval.

Multivariate logistic regression model (dependent variable, steroid treatment, immunosuppressive therapy, and abdominal surgery; independent variables entered in the model, gender, age at diagnosis, disease location, disease behavior, extraintestinal manifestations, abdominal abscess, perianal disease, steroid dependence (for immunosuppressive treatment and abdominal surgery), steroid resistance (for immunosuppressive treatment and abdominal surgery), immunosuppressive therapy (for abdominal surgery). Hosmer and Lemeshow test (P = 0.555). Discriminative power (area under the ROC curve = 0.623; 95% CI 0.586–0.659) for steroids. Hosmer and Lemeshow test (P = 0.106). Discriminative power (area under the ROC curve = 0.807; 95% CI 0.783–0.831). For immunosuppressive treatment. Hosmer and Lemeshow test (P = 0.945). Discriminative power (area under the ROC curve = 0.867; 95% CI 0.847–0.888), for surgery.

*Reference categories for OR estimation.

types and genotypes.[1] In our population, A1 patients appear to be a different CD group. They were more often steroid-dependent and immunosuppressed and they had more EIMs. This is in agreement with previous studies which report a more severe phenotype with steroid resistance and a greater need for immunosuppression.[6] These findings further emphasize the need for early steroid-sparing medications in pediatric IBD. As opposed to what could be expected, we observed a low frequency of patients with a family history (7%) of CD in the pediatric group, thereby suggesting that genetic factors are not as important in the early onset phenotype and suggesting that pediatric IBD is still evolving, and points to environmental factors contributing to its pathogenesis.

Patients with disease diagnosed after 40 years of age, in agreement with a previous study,[7] were less frequently steroid-dependent, and consequently, immunosuppression and biologic therapy was less often prescribed. However, in our study group we did not find a tendency for a decreased rate of abdominal surgery, as reported before.[8] With respect to disease location, the most important difficulty with the Vienna Classification arose with the inability of allowing upper GI involvement to coexist with distal disease. The Working Party of the 1998 Vienna World Congress of Gastroenterology,[9] reported that 7% of patients were reported as L4, but in the presents series only 1% of our patients had exclusive location in the upper digestive tract. This is similar to a previous study from Freeman,[10] who reported a low exclusive involvement of the upper digestive tract (0.8%). Thus, the majority of patients who have upper GI tract involvement also have disease in other locations. In the present series, 3.3% of upper GI tract involvement was associated with ileal location ($L1_4$), 1.5% was associated with colonic disease ($L2_4$), and 0.4% with ileocolonic disease ($L3_4$). Overall, 5.2% of patients included in this study had upper GI tract involvement, although these numbers might change with the wider utilization of wireless capsule endoscopy.

Also, in the Vienna Classification perianal fistulizing disease was included in the penetrating behavior group, but the Working Party felt that perianal disease requires separate subclassification.[1] In our cohort, 38% of patients had nonstricturing and nonpenetrating disease, while 26% were classified as stricturing and 36% as penetrating. As 4% of patients had perianal disease without any more abdominal penetrating events, in the present series we may admit that 4% of patients would be erroneously classified as penetrating disease according to the Vienna Classification.

CD location changes only minimally over time, as opposed to the disease behavior changing from pure inflammatory to stricturing or fistulizing disease, with almost 90% of patients progressing to complicated behavior after 20 years of disease.[11,12] All these arguments favor the hypothesis that if we become accustomed to categorizing CD according to the Montreal Classification, in terms of location and age of onset, we may very well be able to predict which is the most probable outcome in the coming years, namely, need for steroids, immunosuppressants, and/or surgery. In this work to put out changes in location and behavior in the first years of disease, we only included patients with more than 5 years of disease. We observed that, in agreement with previous studies,[13] ileal involvement was associated with the need for surgical interventions, as opposed to ileocolonic and upper digestive tract involvement, which were associated with immunosuppression. If we consider the severity index used herein, the Silverstein et al[4] modified categorization, which basically reflects the step-up policy that most physicians still use when treating CD, in ascending order sulfasalazine, 5-aminosalicylate, corticosteroids, immunosuppressants, and surgery, we found that disease phenotype, location, and age of disease onset were associated with different disease severity categories.

Finally, we would like to emphasize that in the present series, 78% of our patients had been on steroids, at least once, 49% had taken immunosuppressants at some point of their disease, and at least 48% submitted to surgery. Less than 10% of CD patients persisted without steroids, immunosuppressants, or abdominal surgery. These numbers are quite similar to previous series published from North America or from Denmark,[14–19] and do not support the study by Wolters et al,[2] where the authors concluded that southern CD had a milder course as compared to patients from northern Europe. They reported a phenotypic north-to-south gradient in CD, illustrated by higher surgery risks in some northern European centers, whereas patients from southern Europe were more likely to pass from severe disease to a milder state, and from there back to the no-medication state. However, it is important to recall that in the Wolters et al study[2] there were only 13 Portuguese patients included. In a recent study from only one hospital in Portugal (quaternary medical center of IBD in the north), only 10% of patients maintained a long-term remission free of steroids after their initial presentation.[20] Thus, according to the present results, we believe that rates of aggressive medical therapy and the need for surgical interventions are very similar to the ones observed and reported in northern European countries.

In conclusion, we were able to clearly demonstrate that there are prognostic differences in the subgroups of patients allocated by the Montreal Classification. Our study shows that stratifying CD patients with respect to disease location as well as age of disease onset may prove useful in predicting the subsequent course in terms of steroids requirement, immunosuppression, and/or surgical interventions. Furthermore, we also want to emphasize that this is probably the largest study coming from a country in southern Europe. In contrast to what had been reported previously, but similar to the series from northern Europe, only a minority of patients will have mild disease.

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