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## Clinical practice in Crohn's disease in bordering regions of two countries: Different medical options, distinct surgical events

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## Abstract

Contemplating the multifactorial nature of Crohn's disease (CD), the purpose of this study was to compare two neighbouring CD populations from different nations and examine how clinical characteristics of patients can influence therapeutic strategies and consequently different surgical events in routine clinical practice. Cross-sectional study based on data of an on-line registry of patients with CD in northern Portugal and Galicia. Of the 1238 patients, all with five or more years of disease, 568 (46%) were male and 670 (54%) female. The Portuguese and Galician populations were similar regarding Montreal categories, age at diagnosis, and years of follow-up. Galician B2 patients were associated with immunosuppression (OR 3.6; CI 2.2–6.1) and biologic treatment (OR 1.8; CI 1.0–3.1). In both populations ileocolonic disease was associated with immunosuppression and biologic treatment and the penetrating group was linked to immunosuppression. In the north of Portugal 47% and 16% of patients, and in Galicia 63% and 33%, were treated with immunosuppressants and biologic treatment, respectively. In the north of Portugal 44% of patients classified as stricturing behavior were operated without immunomodulation, in contrast to 12% in Galicia. In the latter it was possible to maintain 16% of B2 patients and 40% of B3 patients without surgery with adequate immunosuppression and/or biologic treatment. The delta of surgeries in B2 patients was 8% and in B3 26%.

**Conclusions:** Stratifying patients according to the Montreal classification identified similar clinical patterns in disparate geographic populations, and revealed that differing medical therapeutic practices may influence the occurrence of surgical events.

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## 1. Introduction

Crohn's disease (CD) is a chronic inflammatory disease characterized by significant morbidity due to frequent intestinal resections and hospitalizations. Despite major developments in the comprehension of the complex pathophysiology of CD there is still no cure for the disease. Furthermore, hospitalization costs, including surgery, comprise 56%–63% of the total direct costs<sup>1,2</sup> as consistently cited in the literature.

Surgery is not a curative option and new lesions can be seen on endoscopy some months following surgery.<sup>3</sup> The goal of treatment in CD is, therefore, to slow or even stop this progression. Thus, the choice of drugs in CD must be timely if one considers that longer disease duration inevitably leads to more irreversible damage. This becomes clear when reflecting on the response to azathioprine in adults who as children were treated early<sup>4,5</sup> or the response to anti-TNF in individuals with shorter disease duration.<sup>6</sup>

Scandinavian countries exhibit a higher incidence as well as more aggressive behavior when compared to patients from Southern Europe,<sup>7</sup> nevertheless our group showed recently that rates of aggressive medical therapy and need for surgical interventions are very similar<sup>8</sup> to the ones obtained from Northern European countries.<sup>9–14</sup>

The north of Portugal and Galicia (North-West of Spain) are two adjacent areas politically separated for the last six centuries. Nonetheless, they are linked due to similar language, culture and traditions. Two independent studies searching for NOD2/CARD15 mutations in CD patients in the north of Portugal and Galicia did not show important genetic differences,<sup>15,16</sup> indicating a similar genetic background.

The intention of the present study was to apply the Montreal classification in a large population of Portuguese and Spanish patients with CD chosen from several centers and identify similarities, and if so, analyse how clinical characteristics of patients could influence therapeutic strategies and subsequently different surgical events in everyday medical practice.

## 2. Patients and methods

### 2.1. Patient inclusion

During a 15 month period (September 2005–December 2006) Portuguese doctors following patients with inflammatory bowel disease (IBD) had the opportunity to collect clinical data and send it to a central database via internet. (<http://www.gedi.med.up.pt/>). In both populations there was no selection of patients. The population of CD patients is

composed of all those observed in the hospitals during the inclusion period. Patients in routine consult, hospitalized, submitted to surgery and those admitted to the emergency room were included. There were no Portuguese patients included in randomized, prospective and double blind trials and, in Galicia, the number of patients included in this trials was scarce (less than 0.5%). Patient registration was carried out through a web-based system with password and user name validated by a scientific committee. The database was approved by national authorities and was supported by the Portuguese group of studies of IBD (GEDII). From this pool only subjects belonging to the North of Portugal were selected, thereby including all patients from hospitals situated north of the Douro River. Twenty-one doctors participated in the study. CD patients were comprised from two third level Hospitals (Sao Joao Hospital of Porto and Santo Antonio Hospital of Porto) (68%), four second level Hospitals (Guimaraes, Paredes, Vila Real and Braga) (31.5%), and private physicians (0.5%). In Portugal the first level hospitals refer their IBD patients to a highest level hospital. A small percentage (1.7%) was included by pediatricians working in reference pediatric centers. These figures represent about 50% of the calculated number of Portuguese patients with IBD. During a similar time period, Galician doctors following patients with IBD had the opportunity to collect clinical data and send it to a central data base via internet (<http://www.alceingenieria.net>). Patient registration was carried out through a web-based system with password and user name validated by a scientific committee. The database was supported by the Galician group of studies of IBD (EIGA). Patients from Galicia (Spain) were included from four reference hospitals (University Hospital of Santiago, Pontevedra Hospital, Arquitecto Marcide Hospital from Ferrol and Xeral Cies Hospital from Vigo). No patients from private practices were included. These four hospitals have a Monographic Inflammatory Bowel Disease Unit and are all third level centers, receiving patients with CD or ulcerative colitis (UC) from smaller centers (called Comarcal Hospitals or first or second level Hospitals).

The information used to complete the data was acquired from clinical charts during a routine medical examination. Several conferences were held with members of both nations in order to standardize and clarify the different parameters used. The diagnostic criteria for CD were based on a suggestive clinical history associated with endoscopic and histological signs of inflammation of the mucosa, after infectious disease was excluded by culture and microscopic stool examination.

Instructions and criteria definitions were posted online and all participants had at least three meetings per year to discuss the inclusion criteria. Patients included in the present study had to fulfill strict international diagnostic criteria for IBD<sup>17</sup> as well as have at least two criteria of the *Copenhagen Diagnostic Criteria of CD*.<sup>17</sup>

## 2.2. Data collection

Information on date of onset of symptoms and diagnosis, type of clinical onset, extent of disease, family history 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 fistulae, clinical course, response to steroids, immunosuppression and/or biologic treatment, as well as previous abdominal or anal surgery was gathered. Abdominal surgery was defined as submission to surgery for intestinal resection, abscess drainage, stricturoplasty, or another procedure such as apendectomy or acute abdomen without intestinal resection (*i.e.* diagnosis of CD without resection). The Montreal classification<sup>18</sup> was used. According to this classification, L4 is a modifier that can be added to L1–L3 when concurrent upper gastrointestinal disease is present. Behavior was defined as B1 when non-stricturing and non-penetrating, B2 when stricturing, B3 when penetrating and *p* is added to B1–B3 when concomitant perianal disease is present. Patients were defined as steroid dependent when unable to taper the prednisolone dose below 10 mg/day or when requiring two or more steroid treatments (1 mg/kg) within a six month period. Steroid resistance was stipulated as the incapability of induce remission with steroids in a dose of 1 mg/kg/day. Patients who had received azathioprine, 6-MP, cyclosporine, or methotrexate were considered in the group of immunosuppression.

## 2.3. Disease severity

Patients were categorized in six disease severity groups, according to the modified Silverstein et al.<sup>19</sup> 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 steroids necessitating a dose of prednisolone above 10 mg/day or two or more steroid treatments within a period of six 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 that required surgical treatment and in addition to immunosuppressants and biologic treatment.

## 2.4. Statistics

Kolmogorov–Smirnov test was used to test for normality. When testing hypotheses regarding continuous variables, parametric tests (student's *t* test and one factor analysis of variance – ANOVA) and nonparametric tests (Mann–Whitney and Kruskal–Wallis tests) were used as appropriate, taking into account normality assumptions and number of groups compared. When examining hypotheses concerning categorical variables Chi-square test and Fisher's exact test were used appropriately. In order to thoroughly grasp the factors associated with the use of steroid therapy and immunosuppression, univariate and multivariate logistic regression modelling was used. In the multivariate logistic regression models the dependent variables were immunosuppression and biologic treatment. Model's goodness-of-fit was assessed using the Hosmer–Lemeshow statistic and discriminative power was evaluated by ROC curve analysis. Influence of outlier data values on model fit was estimated using leverage statistics, and

**Table 1** Baseline population characteristics.

	$\Sigma n$ (%)	North Portugal	Galicia	<i>p</i>
Gender, <i>n</i> (%)				
Male	568 (46)	318 (42)	250 (51)	<b>0.002<sup>a</sup></b>
Female	670 (54)	433 (58)	237 (49)	
Family history of IBD, <i>n</i> (%)				
Yes	139 (13)	59 (10)	80 (16)	<b>0.001<sup>a</sup></b>
Age at diagnosis, <i>n</i> (%)				
≤ 16 years	104 (8)	59 (8)	45 (9)	0.632 <sup>b</sup>
17–40 years	898 (73)	550 (74)	348 (71)	
> 40 years	233 (19)	139 (19)	94 (19)	
Age, median (P25–P75)	28 (21–37)	29 (22–37)	27 (20–37)	0.051 <sup>b</sup>
Years of disease median <sup>c</sup> (P25–75)	10 (7–15)	10 (7–15)	10 (7–15)	0.454 <sup>b</sup>

<sup>a</sup> Chi-square test.<sup>b</sup> Mann Whitney test.<sup>c</sup> Median (percentile 25–percentile 75) after diagnosis.

collinearity was assessed by evaluating coefficients correlation matrix. Due to multiple hypothesis tests performed and presented in this study, inflation of type I error is a risk. Whenever statistical hypothesis testing is used and taking into consideration 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 Version 15.0 for Windows (SPSS®).

### 3. Results

#### 3.1. Analysis of Montreal categories

The database population of 1238 patients with CD was composed of 568 (46%) males and 670 (54%) females with a mean age at diagnosis of 28 years (percentile 25–21 and

percentile 75–37) and a median time after diagnosis of 10 years (percentile 25–7 and percentile 75–15) (Table 1). Only patients with five or more years of disease were included in this analysis because this period is necessary to properly classify disease behavior. This approach seems to be imperative when results from different centers are compared. Regarding age at diagnosis, 8% were classified as A1 (below 16 years), 73% as A2 (17–40 years), and 19% as A3 (above 40 years). Portuguese and Spanish populations were alike in relation to Montreal age categories, age at diagnosis, and years of follow-up. A predominance of females were in the North of Portugal, whilst, in the North of Spain, patients presented more frequently a positive family history of IBD (10% vs. 16%,  $p<0.001$ ). This difference was clearly evident in A1 and A2 groups (8% vs. 22% and 10% vs. 16%).

Table 2 shows the categorization of patients according to the Montreal classification. The verisimilitude of the allocation of patients to the different categories of location in both countries was noteworthy. No differences were found

**Table 2** Contingency table for Montreal classification and medical and surgical treatments.

	$\Sigma n$ (%)	North Portugal	Galicia	<i>p</i> <sup>a</sup>
Classification				
B1 + B1p	485 (45)	263 (44)	222 (46)	0.097
B2 + B2p	270 (25)	142 (24)	128 (27)	
B3 + B3p	325 (30)	197 (33)	128 (27)	
Localization				
L1 + L14	489 (40)	302 (41)	187 (39)	0.268
L2 + L24	261 (21)	165 (22)	96 (20)	
L3 + L34	466 (38)	269 (37)	197 (41)	
Upper digestive track involvement <i>n</i> (%)	60 (5)	42 (6)	18 (4)	0.130
Immunosuppression <i>n</i> (%)	662 (54)	356 (47)	306 (63)	<0.001
Biologic treatment <i>n</i> (%)	283 (23)	123 (16)	160 (33)	<0.001
Abdominal surgery <i>n</i> (%)	510 (41)	324 (43)	186 (38)	0.077

<sup>a</sup> Chi-square test.

**Table 3** Contingency table for Montreal age categories and medical and surgical treatments.

	Age at diagnosis								
	≤ 16 years			17–40 years			>40 years		
	North Portugal	Galicia	<i>p</i> <sup>a</sup>	North Portugal	Galicia	<i>p</i> <sup>a</sup>	North Portugal	Galicia	<i>p</i> <sup>a</sup>
Immunosuppression <i>n</i> (%)	38 (64)	28 (62)	0.819	263 (48)	228 (66)	<0.001	54 (39)	50 (53)	0.034
Biologic treatment <i>n</i> (%)	14 (25)	15 (33)	0.358	87 (16)	122 (35)	<0.001	22 (16)	23 (24)	0.101
Abdominal surgery <i>n</i> (%)	19 (32)	11 (24)	0.387	263 (48)	141 (41)	0.030	41 (30)	34 (36)	0.302

<sup>a</sup> Chi-Square test and Fisher's Exact Test.

regarding upper digestive track involvement. In relation to behavior categories, the B1+B1p (non-stricturing, non-penetrating) phenotype was found in 45% of patients, B2+B2p (stricturing) in 25%, and B3+B3p (penetrating) in 30%. The distribution was identical in both countries.

### 3.2. Analysis of treatment according to age of onset of CD

Overall, there is a trend favouring Portugal for more surgeries (43% vs. 38%); on the other hand the Galician population was more frequently submitted to immunosuppression and biologic treatment. Immunosuppression, biologic treatment, and surgery were similar between two populations in the A1 group (Table 3); however the therapeutic strategy was different among A2 patients. Attesting to this fact, the Galician A2 group of patients was found to have received more often immunosuppressant therapy (48% vs. 66%, north

of Portugal and Galicia, respectively) and biologic agents (16% vs. 35%, north of Portugal and Galicia, respectively), and, interestingly, were less frequently submitted to surgery (48% vs. 41%, the north of Portugal and Galicia, respectively) (Table 3).

### 3.3. Severity

Table 4 shows severity of disease in six different categories according to the Silverstein et al. modified classification.<sup>19</sup> In regards to the age of onset, 59% of patients from the A1 group were considered as severe and 67% and 62% of those classified as B2 and B3, respectively, had undergone surgery. On the whole, the panorama was not altered when the patients were stratified by location, as 43% and 40% of those allocated in L1 and L3 groups, respectively, were operated. Globally, 39% of patients in the B2 group and 62% in the B3 group needed immunosuppression and/or biologic

**Table 4** Contingency for age at diagnosis, location and behavior according to treatment – classified in six disease severity categories (modified Silverstein et al.<sup>19</sup> classification).

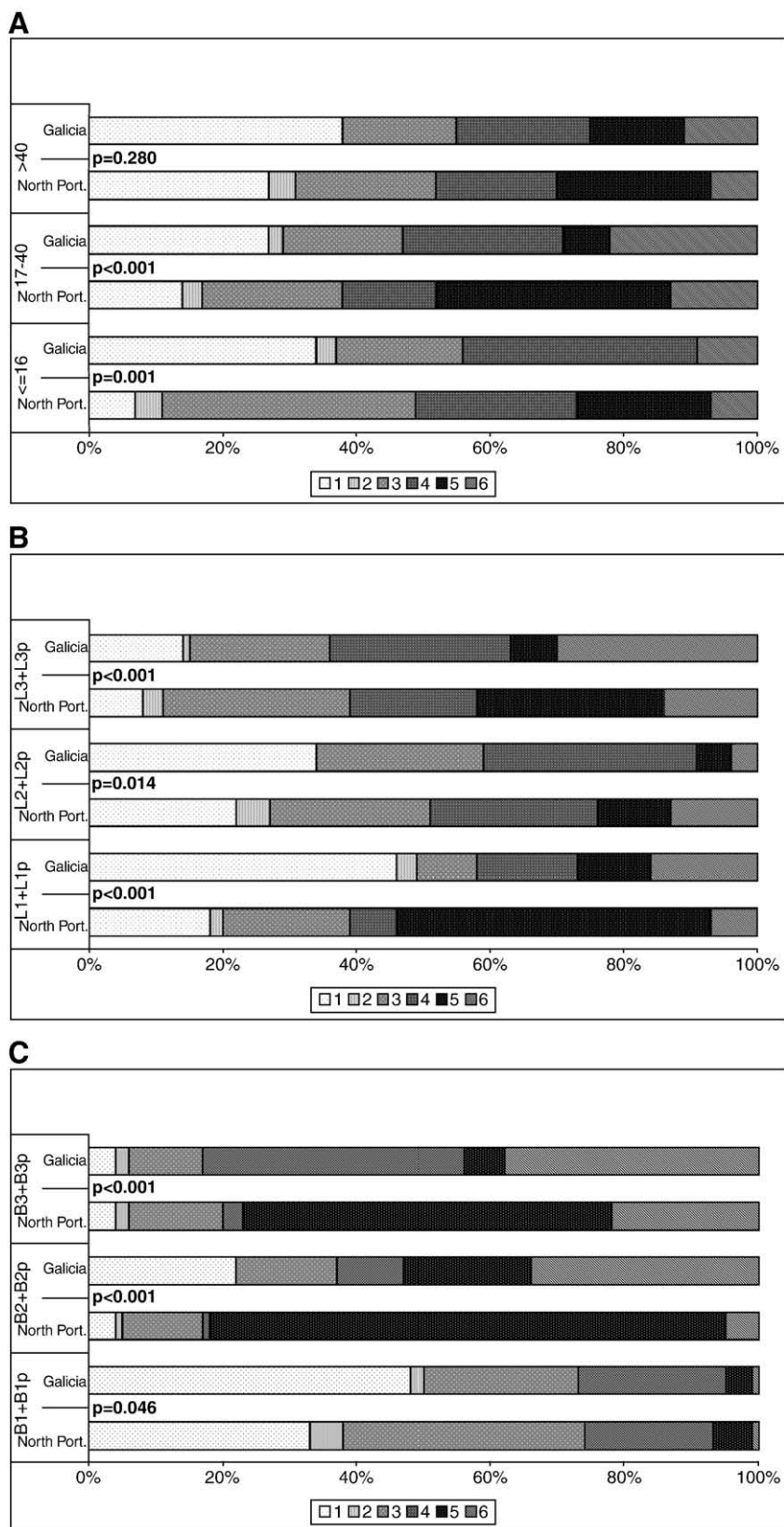
	Silverstein score												<i>p</i> <sup>a</sup>
	1		2		3		4		5		6		
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Age at diagnosis, <i>n</i> (%)													
≤ 16 years	14	(18)	3	(4)	24	(31)	22	(28)	9	(12)	6	(8)	0.001
17–40 years	115	(20)	16	(3)	116	(20)	105	(18)	133	(23)	98	(17)	
>40 years	49	(32)	3	(2)	30	(19)	29	(19)	29	(19)	14	(9)	
Classification													
B1+B1p	135	(41)	12	(4)	97	(29)	68	(21)	16	(5)	3	(1)	<0.001
B2+B2p	20	(13)	1	(1)	22	(14)	9	(6)	77	(48)	30	(19)	
B3+B3p	9	(4)	4	(2)	27	(12)	43	(20)	70	(32)	67	(30)	
Localization													
L1+L14	90	(29)	7	(2)	48	(15)	32	(10)	101	(32)	33	(11)	<0.001
L2+L24	52	(27)	6	(3)	47	(24)	54	(28)	16	(8)	17	(9)	
L3+L34	32	(11)	6	(2)	73	(25)	69	(23)	52	(18)	65	(22)	

Legend: 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 two or more steroid treatments within a period of six 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 finally score 6 for severe refractory disease which required surgery and also immunosuppressants and biologic treatment.

<sup>a</sup> Pearson chi-square test.

treatment. Finally, the majority of L3 patients required immunosuppression with or without biologic treatment (70%).

When the clinical practice of each region was analyzed (Fig. 1A), taking into account age categorization, there was a striking trend towards submitting the patients in the North of



**Table 5** Contingency for age at diagnosis, location and behavior according to surgery, immunosuppression and biologic treatment.

	Surgery without BT or IS			Without surgery and with BT and/or IS		
	North Portugal	Galicia	<i>p</i> <sup>a</sup>	North Portugal	Galicia	<i>p</i> <sup>a</sup>
Age, <i>n</i> (%) <sup>b,c</sup>						
≤ 16 years	9 (15)	0 (0)	<b>0.005</b>	29 (50)	18 (40)	0.209
17–40 years	115 (21)	18 (5)	<b>&lt;0.001</b>	115 (21)	110 (32)	<b>&lt;0.001</b>
>40 years	19 (14)	10 (11)	0.547	34 (25)	27 (29)	0.282
Behavior, <i>n</i> (%) <sup>c</sup>						
B1+B1p	9 (3)	7 (3)	1.000	89 (34)	82 (37)	0.505
B2+B2p	62 (44)	15 (12)	<b>&lt;0.001</b>	11 (8)	21 (16)	<b>0.038</b>
B3+B3p	64 (33)	6 (5)	<b>&lt;0.001</b>	19 (10)	51 (40)	<b>&lt;0.001</b>
Location, <i>n</i> (%) <sup>c</sup>						
L1+L14	88 (29)	13 (7)	<b>&lt;0.001</b>	51 (17)	31 (17)	1.000
L2+L24	12 (7)	4 (4)	0.425	54 (33)	47 (49)	<b>0.012</b>
L3+L34	41 (15)	11 (6)	<b>0.002</b>	71 (27)	76 (39)	<b>0.007</b>
Follow-up, years <sup>d</sup> (P25–P75)	12 (8–19)	14 (9–25)	0.088	9 (7–13)	9 (7–14)	0.987

<sup>a</sup> Pearson chi-square test.

<sup>b</sup> Age at diagnosis.

<sup>c</sup> Percent of patients in each category according to surgery without biologic treatment (BT) and immunosuppression (IS) and patients without surgery and medically treated with biologic or immunosuppression.

<sup>d</sup> Median (percentile 25–percentile 75) after diagnosis.

Portugal to surgery without previous immunosuppression, particularly evident in B2 and B3 groups (Fig. 1C). When the patients were grouped by location the differences between the two regions were essentially observed in the L1 population, highlighting the frequent tendency to operate in the Portuguese group (Fig. 1B).

In Galicia it was possible to avoid surgery in a significant proportion of patients. The strategy between the two regions is undoubtedly diverging and, in Galicia, 16% of the stricturing patients persist without surgery (Table 5) with adequate medical treatment (delta of surgeries between the two populations of 8%) (Fig. 2B). In the same line of thoughts, in Galicia the majority of patients in the penetrating group (40%) were likely to preserve their intestine without surgery (delta of surgeries 26%, Fig. 2C). Lastly, concerning disease onset, in A2 and A3 groups the difference between Portugal and Galicia was 7 and 8%, respectively (Fig. 2A).

### 3.4. Univariate and multivariate analysis of factors associated with immunosuppression, biological treatment and abdominal surgery

Table 6 shows the variables which were associated with the use of immunosuppressants and biologic therapy, on uni and multivariate analysis. The A1 Portuguese group was more frequently associated with immunosuppression. Regarding the B3 group, these patients were clearly more often treated with

immunosuppression in both populations, and more frequently submitted to biologic treatment in the Galician population. It is particularly important to emphasize that the Galician B2 patients were significantly associated with immunosuppression (OR 3.685; CI 2.206–6.154) and biologic therapy (OR 1.830; CI 1.061–3.156).

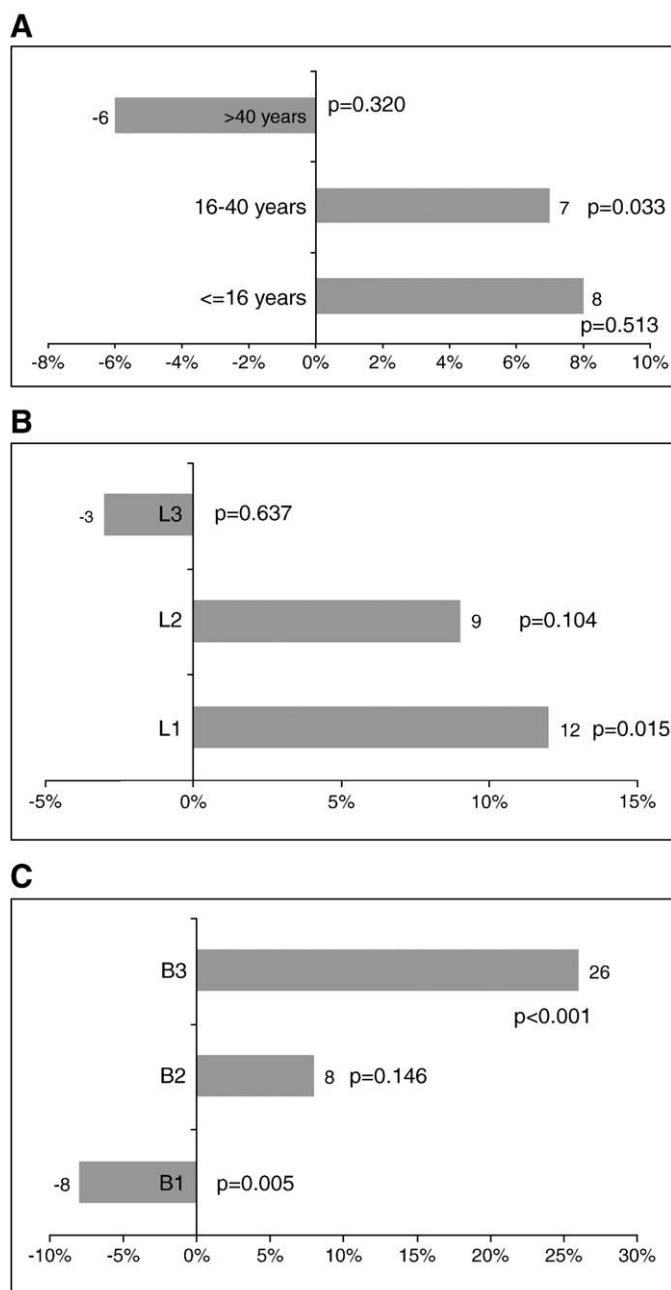
Remarkably, when the groups were allocated according to disease location, colon involvement (L2 and L3) was associated with risk of immunosuppression (L2: OR 2.233 CI 1.254–3.975; L3: OR 3.12 CI 1.918–5.079) in Galicia and biologic therapy in both regions.

## 4. Discussion

Northern Portugal and Galicia (North-West of Spain) are two adjoining areas with similar extents and some common epidemiological characteristics such as an Oceanic climate and presence of a large number of coastal villages with similar cultural and food habits. These two regions are politically and economically independent and have different health systems. This study was performed to understand if clinical characteristics of patients were comparable, and if so, to ascertain if different medical strategies could lead to different surgical outcomes.

Based on mesalazine consumption in 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

**Figure 1** Distribution of the Northern Portuguese and Galician CD populations by age at diagnosis (A), location (B) and behavior (C) according to treatment – classified in six disease severity categories (modified of Silverstein et al.<sup>19</sup> 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 two or more steroid treatments within a period of six 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 finally score 6 for severe refractory disease who came to need surgery as well as immunosuppressants and biologic treatment.



**Figure 2** Delta of surgical intervention procedures related with CD in the Northern Portuguese and Galician CD population allocated by age at diagnosis (A), Location (B) and behavior (C).

100,000 inhabitants and in the north of Portugal, there was an estimated 2094 patients. Half of these patients were incorporated into the database.<sup>20</sup> Regarding Galicia, a prevalence of 179 patients per 100,000 inhabitants was estimated<sup>21</sup> and at least half of the population was also included.

The strength of this study lies in the assessment of CD patients in a large scale involving two different countries in actual clinical practice, outside trials. The characteristics of patients in both countries were alike in relation to the background of the patients, as well as, in terms of health care. In Portugal both tertiary and secondary level hospitals were included, as in Galicia where IBD units encompass patients from tertiary and secondary level hospitals. There-

fore, the two groups are hospital based patients covering all of the geographic area of the study.

In both populations a family history rate of 13% was reported, being highest in Galician patients (16%). This fact could reflect an increasing incidence of IBD in Portugal accentuating the role of environmental factors. Among family studies hitherto published, the highest prevalence of IBD among relatives originated from an American study by Farmer et al.,<sup>22</sup> showing a positive family history of 35%. Nevertheless, IBD family history in heretofore reports was 5–20%.<sup>23,24</sup>

All of the Montreal classification categories were parallel. This fact is a strong argument supporting the Montreal classification as a useful instrument in clinical practice permitting a uniform and standardized classification of CD patients.



**Table 6** Univariate and multivariate logistic regression models for factors associated with immunosuppression and biologic treatment.

	Immunosuppression		Biologic treatment	
	Univariate analysis OR (CI 95%)	Multivariate analysis <sup>a</sup> OR (CI 95%)	Univariate analysis OR (CI 95%)	Multivariate analysis <sup>a</sup> OR (CI 95%)
<i>North Portugal</i>				
A1 <sup>b</sup>	1	1	1	1
A2	0.506 (0.290–0.885)	<b>0.373 (0.193–0.723)</b>	<b>0.564 (0.295–1.076)</b>	<b>0.353 (0.130–0.962)</b>
A3	0.355 (0.189–0.669)	<b>0.341 (0.161–0.720)</b>	<b>0.564 (0.265–1.203)</b>	1.579 (0.879–2.835)
L1+L1 <sub>4</sub>	1	1	1	1
L2+L2 <sub>4</sub>	1.170 (0.798–1.714)	1.202 (0.726–1.991)	3.478 (2.064–5.860)	<b>2.776 (1.342–5.744)</b>
L3+L3 <sub>4</sub>	1.626 (1.167–2.265)	<b>1.839 (1.259–2.688)</b>	2.200 (1.338–3.616)	<b>1.987 (1.602–3.717)</b>
B1+B1p	1	1	1	1
B2+B2p	1.053 (0.690–1.608)	1.056 (0.664–1.678)	0.249 (0.095–0.635)	0.389 (0.142–1.061)
B3+B3p	2.358 (1.615–3.443)	<b>2.613 (1.727–3.953)</b>	1.217 (0.716–2.068)	0.780 (0.366–1.664)
<i>Galicia</i>				
A1*	1	1	1	1
A2	1.154 (0.607–2.192)	1.034 (0.501–2.134)	1.080 (0.559–2.084)	1.044 (0.499–2.185)
A3	0.690 (0.334–1.426)	0.554 (0.242–1.269)	0.648 (0.298–1.411)	0.700 (0.294–1.665)
L1+L14	1	1	1	1
L2+L24	1.327 (0.807–2.181)	<b>2.233 (1.254–3.975)</b>	1.591 (0.910–2.781)	<b>2.036 (1.094–3.787)</b>
L3+L34	3.112 (2.010–4.818)	<b>3.121 (1.918–5.079)</b>	3.091 (1.975–4.838)	<b>2.703 (1.667–4.8380)</b>
B1+B1p	1	1	1	1
B2+B2p	2.784 (1.758–4.410)	<b>3.685 (2.206–6.154)</b>	1.522 (0.914–2.535)	<b>1.830 (1.061–3.156)</b>
B3+B3p	9.934 (5.374–18.37)	<b>9.633 (5.065–18.21)</b>	6.742 (4.144–10.970)	<b>6.328 (3.815–10.495)</b>

Legend: OR – Odds Ratio; CI 95% – 95% confidence interval. Discriminative power (Area under the ROC curve = 0.665; CI 95% 0.621–0.709 in North of Portugal and ROC curve = 0.767; CI 95% 0.724–0.811 in Galicia) for immunosuppression. Hosmer and Lemeshow Test ( $p=0.556$  and  $p=0.808$ , North of Portugal and Galicia, respectively). Discriminative power (Area under the ROC curve = 0.675; CI 95% 0.614–0.736 in North of Portugal and ROC curve = 0.739; CI 95% 0.691–0.787 in Galicia) for biologic treatment. Hosmer and Lemeshow Test ( $p=0.779$  and  $p=0.229$ , North of Portugal and Galicia, respectively).

<sup>a</sup> Multivariate logistic regression model (Dependent variable – immunosuppressive therapy and biologic treatment; Independent variables entered in the model – age at diagnosis, disease location, and disease behavior).

<sup>b</sup> Reference categories for Odds Ratio (OR) estimation.

The applicability of clinical trial results to routine clinical practice has been frequently questioned<sup>25</sup> and herein we have the opportunity of view the results of current practice in two populations. In the present series, 14% of CD patients persisted without steroids, immunosuppressants, or abdominal surgery, 54% had taken immunosuppressants at some point of their disease, 23% had taken biologic treatment and 41% were submitted to surgery. These numbers are quite similar to previous series published from North America and from Denmark.<sup>9–14</sup>

We would like to emphasize that regardless of similar Montreal classification and similar geographic location it is apparent that different immunosuppression policies exist in these close regions. In multivariate analysis ileocolonic disease was associated with immunosuppression, and biologic treatment and the penetrating group were related to immunosuppression. Galician patients with only colonic involvement (L2+L2<sub>4</sub>) and stricturing behavior (B2+B2p) were also associated with immunosuppression and biologic treatment. In Portugal, younger patients (disease onset below 16 years) were more often immunosuppressed and

exposed to biologic treatment, as in concurrence with earlier studies which described a more severe phenotype with steroid resistance, and a greater need for immunosuppression<sup>26</sup> in the pediatric IBD population. In addition, Beaugerie et al.<sup>27</sup> reported an initial young age of onset (below 40 years) and localization of the disease restricted to the colon as risk factors associated with disabling disease. More recently,<sup>28</sup> ileo-colonic location was linked to a more aggressive progression. In same study, and in agreement with ours, stricturing behavior and weight loss (>5 kg) at diagnosis were independently associated with the time to development of severe disease.

These disparities concerning clinical use of immunomodulation and biologic drugs are remarkable and could be explained by that fact that all Galician patients belong to IBD units. In these units, doctors and nurses are familiarized with these drugs and patients can directly contact their physicians by phone or by open access to the hospital. In the north of Portugal gastroenterologists are not exclusively dedicated to IBD and this could delay the early introduction of immunosuppressants and biologic drugs. In this context

there are several reasons to consider that IBD units are essential in modern IBD practice. They permit the treatment of difficult patients<sup>29</sup> and are cost effective by providing open access, subsequently reducing the rates of surgeries and long hospitalizations.<sup>30</sup> Likewise, most of A1 patients from the north of Portugal came from an IBD specialized unit with pediatricians devoted to gastroenterology and IBD and, as such, presented a higher prevalence of immunosuppression (64%).

Approximately three quarters of CD patients are hospitalized for medical management<sup>31</sup> and many require several surgeries.<sup>32</sup> Medications that can decrease hospitalization and surgery have the potential to diminish the economic burden of the disease.<sup>33</sup> Infliximab<sup>34</sup> and adalimumab<sup>35</sup> were related to a decreased number of CD-related hospitalizations and surgeries, whilst there is some controversy in relation to azathioprine.<sup>36,37</sup> A significant difference between these two populations is the number of surgeries. In general, there is a decrease in the number of surgical procedures in Galicia. In a detailed analysis this is particularly evident in the ileal involvement, in stricturing and penetrating behavior, as well as, in A2 patients. In the north of Portugal, 44% of patients classified as stricturing behavior were operated without immunomodulation when compared to 12% of Galician patients. In the latter region it was possible to maintain 16% of patients without surgery with adequate immunosuppression and/or biologic treatment. Overall, there is a delta of surgeries of 8%. In relation to penetrating patients the differences were more evident. In the north of Portugal, 33% of patients had surgery performed without immunomodulation and, in Galicia, only 5%. Furthermore, it was possible to maintain 40% of B3 patients in Galicia without surgery with adequate immunosuppression and/or biologic treatment. The delta in these patients was 26%. Regarding ileal patients, the pattern was similar. Summing-up, in more aggressive patients, namely penetrating and stricturing behaviors and with ileocolonic disease, timely immunosuppression and biologic treatment avoided the need for surgery. Interpretations made regarding the relationship between surgery and immunosuppression and biologic treatment have some limitations. First, our study is not prospective. Second, it was not clearly possible to know in some patients the date of onset of immunosuppression as well as the median dose of intake. Therefore, the relationship between the duration and dose of azathioprine intake before surgery could not be analyzed. Third, the criteria of introduction of biologic treatment and azathioprine were not homogenous and standardized. Even so, a significant number of patients with similar duration of disease (at least 9 years) persisted without surgery with immunosuppression or biologic treatment. These facts were observed by comparing different realities in two countries aware of the growing tendency towards immunosuppression and biologic treatment<sup>38</sup> in current medical practice.

In conclusion, we clearly demonstrated that stratifying patients according to Montreal classification identified similar clinical patterns in disparate geographic populations, by this means identifying similar prognostic groups. Furthermore, we also emphasize that differing medical therapeutic practice, namely immunosuppression and biologic treatment may influence the occurrence of surgical events.

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