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Article

Characterization of Inflammatory Bowel Disease in the Elderly According to Age of Onset

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Abstract: Background/Objectives: Elderly populations are under-represented in inflammatory bowel disease (IBD) clinical trials, with limited data on phenotype, treatment patterns, outcomes and comorbidities. The main objective of this study was to evaluate, in an elderly cohort with IBD, demographic and disease characteristics, comorbidity, polypharmacy and treatment patterns according to the development of IBD at or before old age. Secondly, the same analysis was done based on the type of IBD: ulcerative colitis (UC) or Crohn's disease (CD). **Material and methods:** Observational, single-center, retrospective study including 118 patients diagnosed with IBD and aged 65 years or older seen at the IBD office of the Regional University Hospital of Malaga between September and November 2022. Data were recorded on demographic, disease-related and IBD treatment-related variables, comorbidities and polypharmacy. A descriptive and analytical study was undertaken according to the age of IBD onset and type of IBD. **Results:** Of the patients included, 50.8% were male, 55.1% had CD and 44.9% UC. IBD onset was before age 65 years in 69.5% and ≥ 65 years in 30.5%. Elderly with IBD who debuted < 65 presented longer disease evolution (19.67 ± 9.82 years) and required more IBD-related surgeries (37.8%); elderly with IBD who debuted ≥ 65 were older (77.69 ± 6.26 years), with no differences in the other variables. According to the type of IBD, elderly UC patients were older (74.55 ± 6.9 years), used more aminosalicylates (77.4%) and had higher rates of polypharmacy (90.6%). Elderly CD patients had higher IBD activity (moderate/severe in 72.3%), used more biologic drugs (58.5%) and required more IBD-related surgeries (44.6%). **Conclusion:** Elderly patients who develop IBD before or after the age of 65 years are overall very similar in baseline and disease-related characteristics. Elderly with CD have higher IBD activity and require more biologic drugs and IBD-related surgeries. Elderly with UC are older and have higher rates of polypharmacy and aminosalicylate use.

Keywords: inflammatory bowel disease; elderly; IBD onset; Crohn's disease; ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease with an uncertain course characterized by recurrent inflammation of the digestive tract. It has periods of worsening of symptoms (flares) interspersed with periods of quiescence or inactivity (remission).

The two main forms of IBD are ulcerative colitis (UC), which principally involves inflammation of the colon mucus layer, and Crohn disease (CD), where involvement of the intestine or colon may be transmural and affect the whole digestive tract, from the mouth to the anus [1].

Although the etiopathogenesis of IBD is not certain, various studies suggest that the disease develops after an interaction between intestinal antigens and intestinal mucus, resulting in increased permeability and an altered barrier function, leading to an excessive immune response in certain patients with a genetic predisposition[2,3]. Other factors, such as diet, smoking, breastfeeding, or the consumption of antibiotics, NSAIDs or contraceptives, also play an important role in disease development [4].

The diagnosis of IBD should be established from a combination of compatible clinical, biochemical, endoscopic, histologic and radiologic findings, there being no gold standard for its diagnosis [5]. An increasing clinical suspicion of IBD, the use of non-invasive markers like fecal

calprotectin, and a greater availability of diagnostic tests such as colonoscopy, have resulted in an increase in the incidence and prevalence of the disease [6,7].

Two peaks have traditionally been described in the development of IBD, one between the ages of 20 and 40 years, and the other between 60 and 70 years, with the latter group comprising 25-35% of all IBD patients [8,9]. In Spain, 1 in each 4 patients with IBD is older than 65 years, thus representing an important proportion of all patients seen at the IBD office. The increase in the number of elderly patients with IBD is partly due to an increased incidence in this age group, as well as the aging of patients with a previous diagnosis of IBD [10,11].

The term older or elderly in IBD usually refers to patients who are older than 60 or 65 years of age, although in some publications it refers to patients older than 70 or even 75 years. Most studies in this age group do not differentiate between older patients with IBD who develop their disease in old age and those who were diagnosed when they were younger and have since aged [12,13]. However, the distinction between these two subgroups can be important, as differences may exist in epidemiology, phenotype, prognosis and specific considerations concerning safety with the available treatments [14].

In general lines, older patients with IBD have an increased risk of severe and opportunistic infections, neoplasms, thromboembolic events, hospitalizations, post-surgical morbidity and mortality, requiring greater consumption of medicines and ambulatory care [15-18]. However, this risk is related with the comorbidity associated not so much with their chronological age but rather with cardiovascular problems, polypharmacy and frailty; factors that have to be considered when treating IBD in the elderly. Special consideration should also be given to the clinical situation and prognostic factors, as with the younger IBD patients.

All these considerations hinder establishment of an optimum treatment strategy to manage IBD in elderly patients [19]. In general, we can state that the efficacy of the drugs available for the treatment of IBD seems similar in both young and old patients, though representation of older patients in clinical trials is scarce [9]. Those studies about the tendencies of treatment in an older population with IBD show a greater use of aminosalicylates and corticosteroids, with a lesser use of immunomodulatory and biological agents, and small molecules, probably due to fear of adverse events [20-22].

Achieving clinical remission in IBD is especially important in this population, thereby reducing the risk of functional worsening and increasing the quality of life of elderly IBD patients, who will have a more active and independent life [19]. All these considerations make it necessary to design new studies on the treatment of the older IBD patient in real clinical practice, helping to define and optimize the therapeutic management of these patients.

Accordingly, we present this study of real clinical practice in a cohort of elderly patients with IBD. The principal objective was to evaluate in this cohort the demographic characteristics, together with data concerning the disease, comorbidity, polypharmacy and treatment patterns depending on the age of onset of IBD, at old age or earlier. As a secondary aim, we undertook the same analysis in the patients according to their type of IBD, UC or CD.

2. Materials and Methods

2.1. Study Population and Design

This observational, single-center, retrospective study was undertaken at the Inflammatory Bowel Disease Unit of the Regional Hospital of Malaga. By consecutive sampling between September and November 2022 a total of 118 patients with IBD, 65 years of age or older, were included in the database. Patients were excluded if they did not have an established diagnosis of IBD or a routine follow-up in the IBD office. The diagnosis of IBD had to be recorded in the clinical history, previously defined according to a combination of compatible clinical, biochemical, endoscopic, histologic and/or radiologic findings.

2.2. Variables

The following variables were recorded in the database:

2.2.1. Principal Variable: Onset of IBD Before or After the Age of 65 Years.

2.2.2. Secondary Variables:

- Demographic: sex, age at last visit, smoking.
- Disease-related: type of IBD (CD or UC), localization in the case of UC (proctitis, left colitis or extensive colitis), localization in the case of CD (ileum, colon, ileocolon or upper intestine), phenotype in the case of CD (inflammatory, stenosing, penetrating or any of the 3 with perianal involvement), years of evolution of the IBD, disease activity at the last visit according to the evaluation of the IBD specialist based on clinical, biological, fecal, endoscopic and/or radiologic data (disease in remission/mild or moderate/severe disease).
- Comorbidities. Graduated according to the Charlson comorbidity index, unadjusted for age, considering comorbidity to be mild (0-2 points), moderate (3-4 points) or severe (>4 points). The Charlson index associates patient comorbidity with long-term death, bearing in mind the presence or otherwise of the following 19 variables: myocardial infarction, diabetes mellitus without organ involvement, diabetes mellitus with organ involvement, congestive heart failure, hemiplegia, peripheral vascular disease, chronic kidney disease, cerebrovascular disease, solid tumor without metastasis, solid tumor with metastasis, leukemia, lymphoma, dementia, chronic obstructive pulmonary disease, connective tissue disease, mild liver disease, moderate or severe liver disease, peptic ulcer and AIDS [23] (Annex 1).
- Polypharmacy and total number of treatments. Based on the total number of chronic active treatments in the health service electronic and intra-hospital prescriptions, polypharmacy was considered to be the use of ≥ 5 treatments. Drugs prescribed for an acute process were not counted in the total number of treatments.
- Treatment-related: active treatment for the IBD, chronic use of aminosalicylates, corticosteroids, topical treatment, immunomodulators, biologic/small molecule treatment and if so, type (anti-TNF, ustekinumab, vedolizumab, tofacitinib), IBD-related surgery.

2.3. Statistical Analysis

A descriptive study was undertaken of all the variables recorded, calculating the absolute and relative frequencies for the qualitative variables and the arithmetic mean and standard deviation (SD) for the quantitative variables. The 95% confidence interval of safety was estimated.

For the bivariate analysis, normality of the sample was assumed as both groups had fewer than 30 subject. The Levene test was used to evaluate homogeneity. As the study design involved independent data with two study groups, the Student t test was used to compare the quantitative variables, the Mann-Whitney U test for the qualitative ordinal variables and the Chi-square test for the qualitative nominal variables, after correction with Fisher's exact test when necessary (if the expected frequency was less than 5). All the contrasts were bilateral and were considered to be significant if the $p < 0.05$. The data were collected, processed and analyzed with IBM SPSS Statistics, version 29.0.1.0 (171).

2.4. Ethical and Legal Aspects

The study was undertaken in accordance with the ethical principles set out in the Declaration of Helsinki. The database was anonymized and only the principal investigator had access to it.

3. Results

A total of 118 patients, aged 65 years or older, with an established diagnosis of IBD were included. Table 1 shows the descriptive characteristics for the whole group.

Table 1. Characteristics of the study population. The results are presented as absolute and relative frequencies (for the qualitative variables) and arithmetic mean plus standard deviation (for the quantitative variables).

	N = 118
Sex	
Male	60 (50.8%)
Female	58 (49.2%)
Age at last visit (years)	72.93 (\pm 6.21)
Smoking	
Yes	24 (20.3%)
No	94 (79.7%)
Type of IBD	
CD	65 (55.1%)
UC	53 (44.9%)
Localization in UC	53 (44.9%)
Proctitis (E1)	10 (8.5%)
Left colitis (E2)	22 (18.6%)
Extensive colitis (E3)	21 (17.8%)
Localization in CD	65 (55.1%)
Ileum (L1)	36 (30.5%)
Colon (L2)	12 (10.2%)
Ileum+colon (L3)	18 (15.3%)
Upper intestine (L4)	0 (0%)
Phenotype in CD	65 (55.1%)
Inflammatory (B1)	30 (25.4%)
Stenosing (B2)	12 (10.2%)
Penetrating (B3)	12 (10.2%)
B1, B2 or B3 with perianal involvement (p)	11 (9.3%)
Onset of IBD	
After age 65 years	36 (30.5%)
Before age 65 years	82 (69.5%)
Years evolution of IBD	15.83 (\pm 10.35)
Charlson comorbidity index	
Mild (0-2 points)	80 (67.8%)
Moderate (3-4 points)	29 (24.6%)
Severe (>4 points)	9 (7.6%)
IBD activity	
Remission/mild	43 (36.4%)
Moderate/severe	75 (63.6%)
Polypharmacy	
Yes	90 (76.3%)
No	28 (23.7%)
Total number of treatments	7.08 (\pm 3.26)
Active treatment for IBD	
Yes	102 (89.8%)
No	12 (10.2%)
Chronic use of aminosalicylates	

Yes	53 (44.9%)
No	65 (55.1%)
Chronic use of systemic steroids	
Yes	14 (11.9%)
No	104 (88.1%)
Use of topical treatment	
Yes	24 (20.3%)
No	94 (79.7%)
Chronic use of immunomodulators	
Yes	18 (15.3%)
No	100 (84.7%)
Use of biologic or small molecule treatment	
Yes	56 (47.5%)
Anti-TNF	15 (12.7%)
Ustekinumab	29 (24.6)
Vedolizumab	12 (10.2%)
Tofacitinib	0 (0%)
No	62 (52.5%)
IBD-related surgery	
Yes	36 (30.5%)
No	82 (69.5%)

Of the 118 study patients, 36 (30.5%) had received the diagnosis of IBD ≥ 65 years (Group 1), and the remaining 82 (69.5%) had been diagnosed with IBD previously and had aged to at least 65 years (Group 2). The demographic characteristics, as well as data concerning disease, comorbidity, polypharmacy and treatment patterns were studied in our elderly IBD patients according to whether they developed the disease in old age or before. Significant differences were found in the variables Need for IBD-related surgery (Figure 1) and Years evolution of the disease, in both cases greater in the group diagnosed with IBD < 65 years; and in the variable Age at last visit, in this case greater in the group diagnosed ≥ 65 years. No significant differences were seen in the other variables. The results of the full analytical study are shown in Table 2.

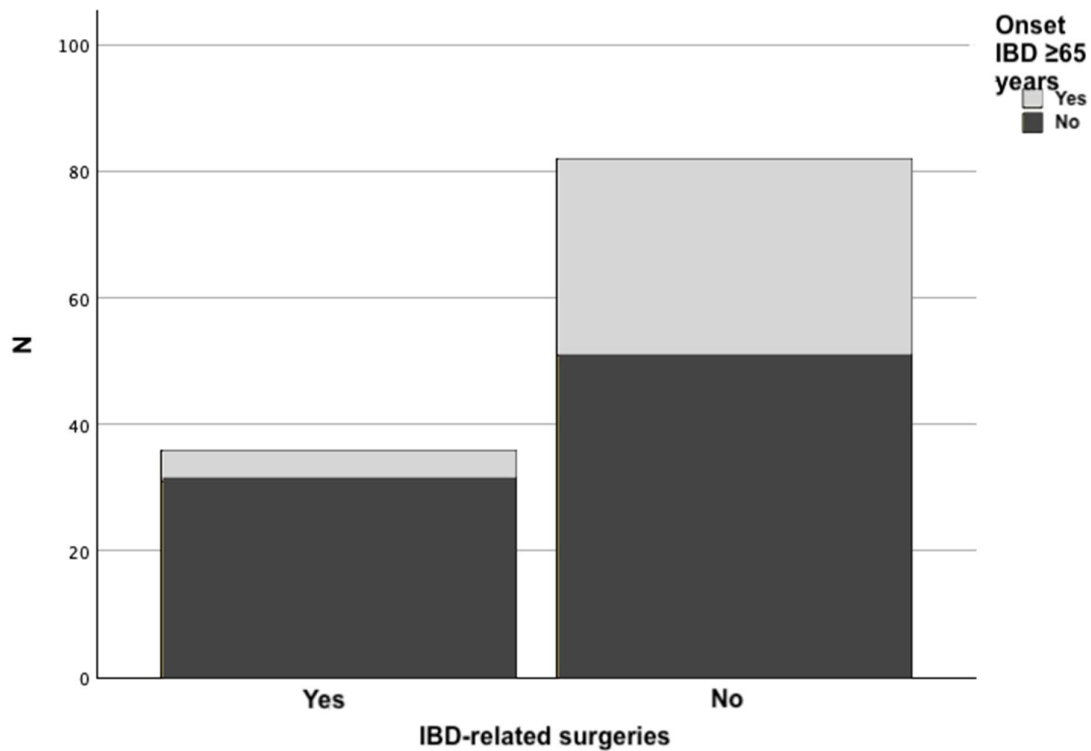


Figure 1. Need for IBD-related surgery according to IBD diagnosis before or after the age of 65 years.

Table 2. Stratified analysis based on age of IBD diagnosis.

	Onset IBD ≥65 years (n=36)	Onset IBD <65 years (n=82)	p-value
Sex			
Male	15 (41.7%)	45 (54.9%)	0.19 ^{a)}
Female	21 (58.3%)	37 (45.1%)	
Smoking	7 (19.4%)	17 (20.7%)	0.87 ^{a)}
Type of IBD			
CD	18 (50%)	47 (57.3%)	0.46 ^{a)}
UC	18 (50%)	35 (42.7%)	
Localization in UC			
E1	4 (22.2%)	6 (17.1%)	0.9 ^{a)}
E2	7 (38.9%)	15 (42.9%)	
E3	7 (38.9%)	14 (40%)	
Localization in CD			
L1	12 (66.7%)	24 (50%)	0.42 ^{a)}
L2	3 (16.7%)	9 (18.8%)	
L3	3 (16.7%)	15 (31.3%)	
Phenotype in CD			
B1	11 (61.1%)	19 (40.4%)	0.24 ^{a)}
B2	4 (22.2%)	8 (17%)	
B3	1 (5.6%)	11 (23.4%)	
B1, B2 or B3 +p	2 (11.1%)	9 (19.1%)	
Polypharmacy	29 (80.6%)	61 (74.4%)	0.47 ^{a)}
Active treatment for IBD	34 (94.4%)	72 (87.8%)	0.34 ^{b)}

Chronic use of aminosalicylates	21 (58.3%)	32 (39%)	0.052 ^{a)}
Chronic use of systemic steroids	5 (13.9%)	9 (11%)	0.76 ^{b)}
Topical treatment	11 (30.6%)	13 (15.9%)	0.07 ^{a)}
Immunomodulators	3 (8.3%)	15 (18.3%)	0.17 ^{a)}
Biologic treatment	14 (38.9%)	42 (51.2%)	0.22 ^{a)}
Type of biologic agent			
Anti-TNF	3 (21.4%)	12 (28.6%)	
Ustekinumab	7 (50%)	22 (52.4%)	0.72 ^{a)}
Vedolizumab	4 (28.6%)	8 (19%)	
IBD-related surgery	5 (13.9%)	31 (37.8%)	0.009 ^{a)}
IBD activity			
Remission/mild	13 (36.1%)	30 (36.6%)	
Moderate/severe	23 (63.9%)	52 (63.4%)	0.96 ^{c)}
Charlson comorbidity index			
Mild (0-2)	25 (69.4%)	55 (67.1%)	
Moderate (3-4)	9 (25%)	20 (24.4%)	0.74 ^{c)}
Severe (>4)	2 (5.6%)	7 (8.5%)	
Age at last visit (years)	77.69 (±6.26)	70.84 (±4.93)	<0.001 ^{d)}
Years evolution of IBD	7.08 (±4.64)	19.67 (±9.82)	<0.001 ^{d)}
Total number of treatments	7.47 (±3.11)	6.91 (±3.32)	0.39 ^{d)}

The results are presented as absolute and relative frequencies (for the qualitative variables) and arithmetic mean plus standard deviation (for the quantitative variables). *p*-values <0.05 are considered statistically significant and appear in bold. ^{a)} Chi-square test; ^{b)} Chi-square test with correction by Fisher's exact test; ^{c)} Mann-Whitney U test; ^{d)} Student t test.

Finally, a second analysis was done, dividing the study population according to type of IBD: Crohn disease (Group 1) or ulcerative colitis (Group 2). The same characteristics were assessed in each group (demographic, disease-related, comorbidity, polypharmacy and treatment patterns). Significant differences were found in the variables polypharmacy, use of aminosalicylates and age at last visit, all greater in the UC group; as well as in the variables disease activity (Figure 2), use of biologic treatment (Figure 3) and need for IBD-related surgery, this time greater in the CD group. Significant differences were also noted in the variable sex, with more women in the CD group and more men in the UC group. No significant differences were seen for any of the other variables. Table 3 shows the results of this second analysis.

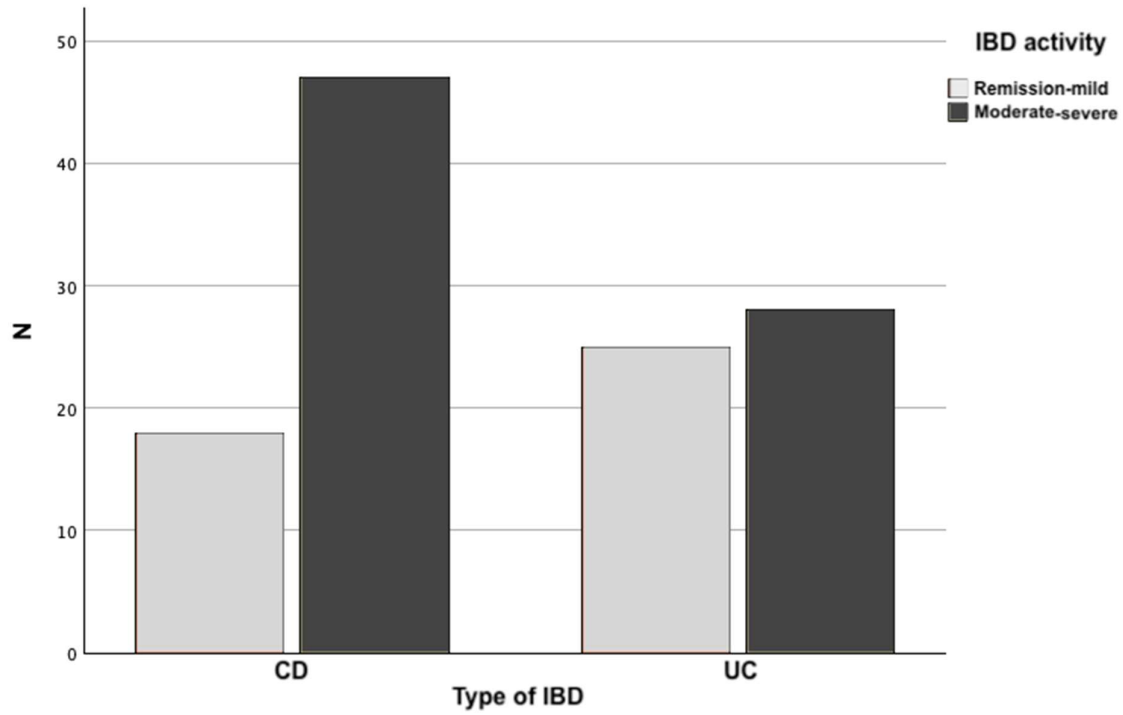


Figure 2. Disease activity according to type of IBD: CD or UC.

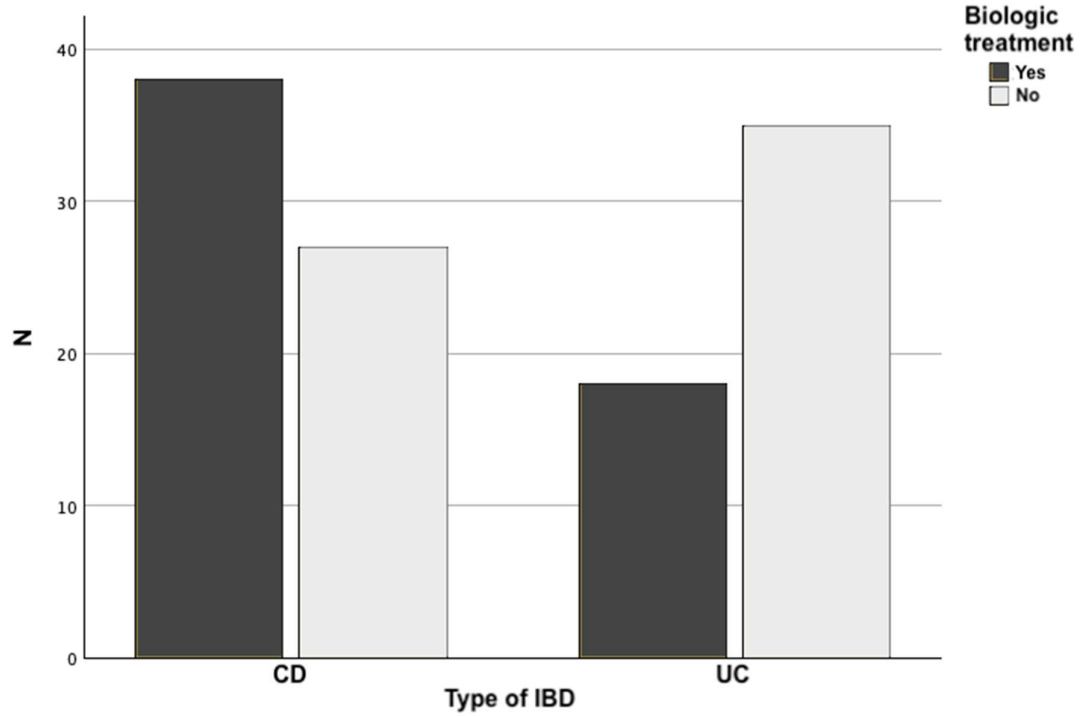


Figure 3. Use of biologic treatment according to type of IBD: CD or UC.

Table 3. Stratified analysis according to type of IBD.

	CD (n = 65)	UC (n = 53)	p-value
Sex			
Male	27 (41.5%)	33 (62.3%)	0.025 ^{a)}
Female	38 (58.5%)	20 (37.7%)	
Smoking	16 (24.6%)	8 (15.1%)	0.2 ^{a)}
Polypharmacy	42 (64.6%)	48 (90.6%)	< 0.001 ^{a)}
Active IBD treatment	56 (86.2%)	50 (94.3%)	0.14 ^{a)}
Chronic aminosalicylates	12 (18.5%)	41 (77.4%)	< 0.001 ^{a)}
Chronic systemic steroids	9 (13.8%)	5 (9.4%)	0.46 ^{a)}
Immunomodulators	13 (20%)	5 (9.4%)	0.11 ^{a)}
Biologic treatment	38 (58.5%)	18 (34%)	0.008 ^{a)}
Type of biologic used			
Anti-TNF	12 (31.6%)	3 (16.7%)	0.48 ^{a)}
Ustekinumab	18 (47.4%)	11 (61.1%)	
Vedolizumab	8 (21%)	4 (22.2%)	
IBD-related surgery	29 (44.6%)	7 (13.2%)	< 0.001 ^{a)}
IBD activity			
Remission/mild	18 (27.7%)	25 (47.2%)	0.029 ^{b)}
Moderate/severe	47 (72.3%)	28 (52.8%)	
Charlson comorbidity index			
Mild (0-2)	45 (69.2%)	35 (66%)	0.84 ^{b)}
Moderate (3-4)	14 (21.5%)	15 (28.3%)	
Severe (>4)	6 (9.2%)	3 (5.7%)	
Age at last visit (years)	71.62 (±5.29)	74.55 (±6.9)	0.013 ^{c)}
Years evolution of IBD	15.98 (±11.05)	15.64 (±9.52)	0.86 ^{c)}
Total number of treatments	6.63 (±3.71)	7.64 (±2.51)	0.082 ^{c)}

The results are presented as absolute and relative frequencies (for the qualitative variables) and arithmetic mean plus standard deviation (for the quantitative variables). P values <0.05 are considered statistically significant and appear in bold. ^{a)} Chi-square test; ^{b)} Mann-Whitney U test; ^{c)} Student t test.

4. Discussion

Elderly patients are poorly represented in clinical trials on the management of IBD. In addition, most relevant studies have focused on the adverse effects in this population of the various therapies available, thus limiting treatment options for older adults [12]. Accordingly, over recent years different papers and guidelines, as well as scientific societies, have published their position papers on IBD in the elderly, attempting to characterize this older population with IBD, identifying their differences in epidemiology, phenotype, prognosis and specific considerations of efficacy and safety of the treatments available [9,12,14,19,20,24].

Concerning epidemiology in this population, our results show a predominance of men in the elder patients with UC, and a predominance of women among those with CD. These results are in agreement with those of Taleban et al.[12] and Sturm et al.[9]

According to various studies,[9,12,14,24] CD in the elderly is more often located in the colon, presenting an inflammatory pattern, whereas UC usually affects the left colon. On the other hand, our study found a predominance of ileal involvement in CD, with an inflammatory pattern, and a similar proportion between left and extensive colitis in UC.

Study of the treatment patterns in our sample showed that almost 80% of the elderly patients with UC were on chronic treatment with aminosalicylates, similar to the percentage reported by

Taleban et al. (84%) [12]. However, this same study reported the use of aminosalicylates in 80% of the patients with CD [12], whereas only 18.5% of our CD patients received this treatment. Chronic systemic steroids were used by 11.9% of our patients, much lower than the percentages reported by Juneja et al.[20] and Parian et al.[19] (35-40%). On the other hand, the use of immunomodulators (15.2%) and anti-TNF agents (12.7%) was greater in our patients than in those of Juneja et al., where immunomodulators were used by just 6% of the older patients with IBD and anti-TNF agents by 9% and 1% of older patients with CD and UC, respectively[20]. Overall, almost half the older population with IBD received biologic treatment, mainly ustekinumab. These differences in prescription patterns may be due to the fact that our sample was collected in a third-level hospital, where the patients have a more aggressive disease or are more difficult to manage.

Another aspect to consider in the treatment of IBD in the elderly is the frequency of polypharmacy, with the consequently greater risk of drug interactions and toxicity. Our study found a 76.3% rate of polypharmacy, with a mean of 7 drugs, more frequently in older UC patients. These results are similar to the prevalence of polypharmacy reported by Parian et al. in their study specifically evaluating this parameter in older patients with IBD (polypharmacy of 85%, with over 40% of their sample taking >10 drugs)[19]; and the mean number of medications reported by Juneja et al. in older patients with IBD (7 ± 3.5)[20].

Concerning the safety of the different treatment regimens, various studies have suggested that advanced age is a risk factor for the development of severe and opportunistic infections in IBD patients treated with corticoids, immunomodulators and anti-TNF biologic agents.[15-18,25] A greater risk has also been reported for lymphomas [26] and skin cancer in older patients with IBD, particularly if they receive treatment with immunomodulators or anti-TNF drugs.[27-29] Nonetheless, this risk is related above all with cardiovascular comorbidity and frailty more than with chronologic age itself, as recently indicated by Kochar et al. in their study comprising over 11000 patients with IBD.[30] Our study found a predominantly mild rate of comorbidity in our older patients with IBD (67.8%), with no obvious differences after stratifying the older IBD patients according to age of onset before or after 65 years.

Distinguishing IBD in the elderly according to whether the onset is before or after 65 years may have important implications for the evolution of the disease and its prognosis, starting with the fact that IBD is usually more aggressive during the first year after its diagnosis and that the risk of infectious complications is greater in the initial months of treatment.[31,32] A retrospective study comparing older patients with IBD who developed the disease before or after 60 years of age showed that the overall disease-related complications were similar in both groups, though treatment-related complications were greater in the patients who developed IBD after the age of 60 years.[33] Our results are similar, showing that both groups (onset before or after 65 years) were comparable regarding the epidemiology, phenotype, disease activity, comorbidity, polypharmacy and treatment patterns.

Finally, concerning the need for surgery related with the IBD, older patients are reported to have greater rates of surgery, mainly soon after the diagnosis.[34-36] Our results, on the other hand, showed a greater need for surgery in the older patients who developed IBD before the age of 65 years, with a longer disease evolution. In our sample, surgery was also more likely to be indicated in those patients with CD (44.6%), who also presented greater disease activity than the patients with UC.

This study, however, has certain limitations related to the fact that it was retrospective and single-center. Nevertheless, it has the strength of being carried out in real clinical practice and that it included a considerable number of patients. Of note, too, is the fact that comorbidity was assessed with the Charlson index, bearing in mind the clinical history of the patients, though in some cases this may not have been up to date. Disease activity was not measured formally with standardized indices, but rather according to the overall assessment of the specialist in the IBD office. We were unable to evaluate treatment adherence by our older patients and, consequently, its importance in the presence or otherwise of polypharmacy. The fact that the study population was taken from a third-level hospital suggests that the sample represents patients with a more aggressive pattern of disease, with a greater use of advanced therapies in the treatment of their IBD (in particular biologic drugs).

5. Conclusions

In our population of older patients who had IBD, no differences were found according to whether they developed the disease before or after the age of 65 years in demography, comorbidity, polypharmacy, treatment patterns, phenotype or disease activity. However, the patients who developed the disease before the age of 65 years had a longer disease evolution and required more surgical procedures. CD was predominant among the study population, more frequently affecting women, presenting a more active course with the need for more biologic treatments and more surgery than the patients with UC, which was more common among older men with greater rates of polypharmacy and greater use of aminosalicylates. There is a high overall use of advanced therapies in the treatment of IBD in the elder patient, particularly biologic drugs.

Author Contributions: M.B.G. has carried out the database creation, data analysis and writing of the paper. R.O.M. and M.J.P. were responsible for the research question, design and revision of the manuscript. All authors are part of the Inflammatory Bowel Disease unit of the centre and have contributed with their experience in the management of disease and interpretation of the data. All authors have read and agreed to the published version of the manuscript

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Informed Consent Statement: As this was a retrospective observational study, no informed consent form was required from the patients included in the study.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest

Institutional Review Board Statement: This study was conducted in accordance with the recommendations of the Declaration of Helsinki and was approved by the Hospital's Research Ethics Committee.

Appendix A

ANNEXES

Annex 1. Charlson comorbidity index: components and score.

Comorbidity	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Peptic ulcer	1
Mild liver disease	1
Diabetes without organ involvement	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end-organ damage	2
Non-metastatic solid tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastasis	6
AIDS	6

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