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Comparative Study on the Management and Outcomes of Postoperative Crohn's Disease in Older Patients: Data From the ENEIDA Registry

Míriam Mañosa[1,2] | Margalida Calafat[1,2] | Elena Ricart[2,3] | Pilar Nos[4] | Eva Iglesias[5] | Sabino Riestra[6] | Francisco Mesonero[7] | Marta Calvo[8] | Jordi Guardiola[9] | Vicent Hernández[10] | Montserrat Rivero[11] | Daniel Carpio[12] | Miguel Mínguez[13] | Cristina Alba[14] | Maria Dolores Martín-Arranz[15] | Milagros Vela[16] | Fernando Gomollón[17] | Santiago García-López[18] | Ana Gutiérrez Casbas[2,19] | Xavier Calvet[2,20] | Carlos González-Muñoza[21] | Jesús Barrio[22] | Javier P. Gisbert[2,23] | Beatriz Sicilia[24] | José Lázaro Pérez-Calle[25] | Luis Bujanda[2,26] | Maria Esteve[2,27] | Laura Ramos[28] | Pilar Varela[29] | Mónica Sierra[30] | Olga Merino[31] | Fernando Bermejo[32] | Manuel Barreiro-de Acosta[33] | Antonio Rodríguez Perez[34] | Lucía Márquez-Mosquera[35] | Orlando García-Bosch[36] | Iago Rodríguez-Lago[37] | Rufo H. Lorente Poyatos[38] | Mariana Fe García Sepulcre[39] | Nuria Maroto[40] | Pablo Vega[41] | David Monfort[42] | Lucía Zabalsa San Martín[43] | David Busquets[44] | Pilar Martinez-Montiel[45] | Joan Riera[46] | Guillermo Alcain[47] | Jordina Llaó[48] | Nacho Marin[49] | Ignacio Marin-Jimenez[50] | Eva Sesé[51] | Manuel Van Domselaar[52] | José M° Huguet[53] | Daniel Ginard[54] | Francesc Bas-Cutrina[55] | Yolanda Ber[56] | Oscar Roncero[57] | Alfredo J. Lucendo[2,58] | Alicia López-García[59] | Margarita Menacho[60] | Pedro Almela[61] | Ángel Ponferrada[62] | Ana Fuentes Coronel[63] | Sergio Maestro[64] | Teresa de Jesús Martínez-Pérez[65] | Carmen Muñoz Vilafranca[66] | Federico Argüelles[67] | Jesús Legido[68] | Pau Gilabert[69] | Mara Charro[70] | Ana M. Trapero[71] | Hipólito Fernández[72] | Santiago Frago[73] | Luis Hernández Villalba[74] | Esther Muñoz[75] | Eugeni Domènech[1,2] | on behalf of the ENEIDA registry of GETECCU

Correspondence: Míriam Mañosa (mmanosa.germanstrias@gencat.cat)

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ABSTRACT

Background: Limited data are available on the management and outcomes of postoperative Crohn's disease (CD) in older patients. We aimed to describe the management of CD in the postoperative setting and assess surgical postoperative recurrence (POR) in this population.

Methods: This was a case-control study including all adult patients with CD from the ENEIDA registry who had undergone a first intestinal resection with ileo-colonic anastomosis. Patients were grouped according to their age at the time of the first surgery in older (over 60 years) subjects and controls (between 18 and 60 years of age).

Results: A total of 3982 (535 older subjects and 3454 controls) underwent a first intestinal resection for CD with an ileo-colonic anastomosis. Time from CD diagnosis to surgery was significantly longer in older patients (114 ± 128 vs. 93 ± 97 months; $p < 0.001$). Older patients also had a lower proportion of penetrating CD (25% vs. 39%; $p < 0.0001$) and perianal disease (14% vs. 25%; $p < 0.0001$). A significantly lower proportion of older patients started preventive therapies for POR (32% vs. 51%; $p < 0.0001$). The cumulative risk of surgical POR was 3.2%, 5.3% and 10.1% in the older group and 3.6%, 6.6% and 14.2% in the control group at three, five and 10 years, respectively ($p = 0.093$). In the multivariate logistic regression analysis, only prevention with thiopurines was associated with a lower risk of surgical POR.

Conclusions: Although postoperative preventive therapy with immunomodulators or biologicals is prescribed less often in older patients after a first intestinal resection, they develop surgical POR as often as younger adult patients.

Key Summary

- What is already known?
  - Crohn's disease (CD) often recurs after intestinal resection, and postoperative recurrence (POR) is a well-recognized clinical challenge.
  - Preventive therapies (e.g., thiopurines, biologics) can reduce surgical POR.
  - Older patients with CD are underrepresented in clinical trials, and their postoperative management is less clearly defined due to age-related concerns about treatment risks and comorbidities.
- What is new here?
  - This large, registry-based study from ENEIDA is the first to specifically compare older (> 60 years) and younger adults (18–60 years) with CD after their first intestinal resection.
  - It reveals that older patients receive significantly less preventive treatment for POR despite having comparable recurrence rates to younger adults.
  - Thiopurines, but not biologics, were independently associated with reduced surgical POR in both groups.
- How can this study help patient care?
  - It highlights a care gap in older CD patients who may be undertreated postoperatively, potentially due to age-related caution rather than clinical need.
  - The findings support reconsidering age-based therapeutic hesitancy.
  - Clinicians can use this evidence to individualize postoperative CD management in older adults by balancing treatment risks with the proven benefits of recurrence prevention.

1 | Introduction

Surgery remains a cornerstone for the management of patients with Crohn's disease (CD) who are intolerant or refractory to medical therapy or in whom intraabdominal fistulizing and stenosing complications occur [1, 2]. Although the availability of biological agents has been associated with a reduction in the rate of early intestinal resections, up to 20% of patients are still operated on within the first 5 years of the disease [3]. Moreover, despite the curative intention of surgery, up to 70% of patients develop new intestinal lesions in the neoterminal ileum within the first year after ileocolic resection if no preventive therapy is started early on, a process known as postoperative recurrence (POR) [4]. Endoscopic POR, defined by the presence of endoscopic lesions in the neoterminal ileum at ileocolonoscopy, precedes the development of symptoms (clinical POR) and may finally lead to a further intestinal resection (surgical POR). For these reasons, current trends point to a more intensive initial medical approach with the aim of preventing disease progression and avoiding repeated surgeries [5–7].

On the other hand, population-based studies reported that up to 10% of new cases of inflammatory bowel disease (IBD) are diagnosed over the age of 60 years [5, 8–11]. In patients with elderly-onset CD, a less aggressive approach might be considered because of the higher risk of infections and malignancies associated with the use of immunosuppressive agents [12–17]. Furthermore, surgical outcomes in older patients may differ from those of young adults [18, 19]. Lakatos et al. [20] reported that old age was a predictive factor of early surgery in CD, probably reflecting a fear of misdiagnosis and a reluctance to prescribe immunosuppressive drugs when surgery is a reasonable alternative. In fact, early surgery has been advised to reduce postoperative complications in older patients [19]. This might explain the similar rates of surgery in young and older patients [21–24] despite the less aggressive phenotype of CD observed among the latter. However, some authors suggest that these comparable outcomes may reflect under-treatment rather than truly milder disease behaviour, as older patients are less likely to receive biologics or undergo surgery due to frailty and comorbidities [25]. Therefore, the notion of a 'less aggressive phenotype' remains uncertain, and further studies are needed to clarify whether these observed differences reflect disease biology or treatment patterns.

In spite of the aforementioned similar or even higher rate of surgery, limited data are available on the postoperative setting of CD in the older population. Therefore, we aimed here to describe the management of CD in the postoperative setting and to assess the rate of surgical POR in patients with CD according to their age at the time of surgery.

2 | Methods

This was a retrospective, multicentre, observational, nationwide study based on the ENEIDA registry (a large, prospectively-maintained database of the Spanish Working Group in IBD –GETECCU-) [26]. The ENEIDA registry was approved by the Research Ethics Committee at all the participating centres. Written informed consent to be enroled in the ENEIDA registry was obtained from all patients. Data extraction was performed in July 2022.

2.1 | Patients

All adult patients with CD in the ENEIDA registry were included if a first ileocolonic resection with ileocolic anastomosis was performed after 2005, when biological therapy was widely used for the management of CD. Only patients with definitive ostomy were excluded. Patients were grouped according to their age at the first surgery; the *older group* included those patients who were operated on over 60 years of age and were compared with adult patients who were operated on between 18 and 59 years of age (*control group*). We used this cut-off point based on what ECCO defines [27]. The older group was subclassified, taking into account age at CD diagnosis, into *long-lasting CD* (if patients were diagnosed before 60 years of age) or *elderly-onset* (if diagnosis occurred over 60 years of age). Patients were followed up until their last visit, surgical POR, or death, whichever came first.

Data collected included age at surgery, gender, smoking habit, phenotypic and clinical characteristics of CD (disease behaviour, extraintestinal manifestations, and perianal disease) and familial history of IBD. For the purposes of the study, the use of thiopurines and biological agents for the prevention of POR

was considered if they were started within 3 months after surgery. Patients on combination therapy (thiopurines or methotrexate plus anti-TNF agents) were considered as anti-TNF treatment.

Surgical POR was defined as a second intestinal resection due to disease-related complications or refractory disease.

2.2 | Statistical Analysis

Continuous variables are expressed as mean with standard deviation or median and interquartile range (IQR) and are compared using non-parametric tests, as needed. Categorical variables are expressed as proportions and compared by means of the Chi-square test. Kaplan–Meier curves were used to evaluate the cumulative probability of surgical POR and were compared between study groups by the log-rank test.

To identify the predictive factors of surgical POR, variables showing a p-value < 0.10 in the univariate analysis were included in a multivariate Cox regression analysis with a stepwise selection of covariates, obtaining for each of them their hazard ratio (HR) with its 95% confidence interval (95% CI).

3 | Results

3.1 | Baseline Characteristics

At the time of data extraction, the registry included 69,740 IBD patients. Among them, 3982 had a diagnosis of CD and a first intestinal resection with ileocolonic anastomosis performed between 2005 and 2020. Of those patients, 535 (13%) underwent surgery when over 60 years of age and 3454 (87%) were adults below 60 years of age (Figure 1).

The baseline characteristics of both study groups are shown in Table 1. Patients in the older group had a significantly lower proportion of ileocolonic disease, fistulizing disease behaviour and perianal disease, but a higher proportion of stricturing disease pattern. Moreover, older patients were less frequently exposed to anti-TNF agents prior to surgery.

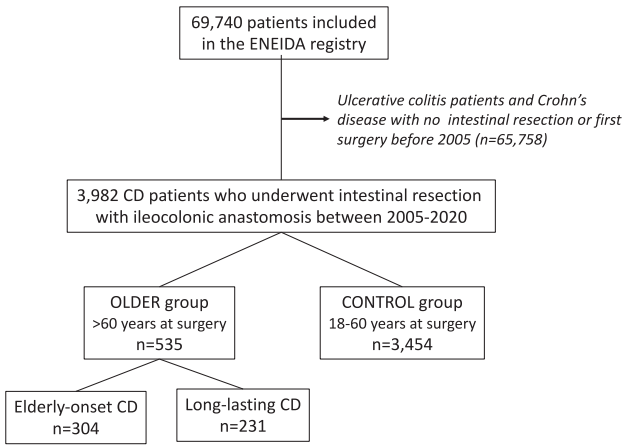

FIGURE 1 | Study flow-chart.

The older group included 304 patients with elderly-onset CD and 231 with long-lasting CD. Patients with elderly-onset CD were older and had a lower prevalence of ileocolonic location, perianal disease and extraintestinal manifestations as compared to long-lasting disease; moreover, patients with elderly-onset CD had been exposed significantly more often to immunomodulators but less to anti-TNF prior to surgery than patients with long-lasting CD. Finally, disease duration was significantly longer among patients with long-lasting CD (Supporting Information S1: Table 1a and 1b,1c).

3.2 | Main Features of the First Ileocolonic Resection and Postoperative Management

Baseline characteristics of the index surgery are shown in Table 2. Although disease duration at the first surgery was longer in the older group as compared to controls, patients with elderly-onset CD were operated on earlier than controls and patients with long-lasting CD (Supporting Information S1: Tables 2a and 2b, 2c). Intestinal stenosis was the main indication for surgery in both study groups, although the proportion of patients operated on due to penetrating complications was significantly higher among the control group. Finally, surgery-related mortality was higher in the older group.

TABLE 1 | Baseline characteristics of the patients.

	Older group ($n = 535$)	Control group ($n = 3454$)	p
Age at index surgery	67.6 ± 10.2	37.7 ± 13.6	< 0.0001
Male gender	259 (48)	1796 (52)	0.12
Active smokers	175 (33)	1032 (30)	0.18
Disease behaviour			
Inflammatory	159 (30)	814 (24)	0.02
Stricturing	242 (45)	1270 (37)	< 0.0001
Fistulizing	134 (25)	1340 (39)	< 0.0001
Location			
Ileal	389 (73)	2215 (64)	< 0.0001
Colonic	15 (3)	72 (2)	0.28
Ileo-colonic	127 (24)	1148 (33)	< 0.0001
Perianal disease ever	77 (14)	865 (25)	< 0.0001
Extraintestinal manifestations	123 (23)	807 (23)	0.93
Familial history of IBD	76 (16)	491 (16)	0.87
Immunomodulators exposure prior to first surgery	366 (68)	2236 (65)	0.097
Anti-TNF exposure prior to first surgery	107 (20)	1599 (46)	0.001

Preventive treatment for POR was prescribed in 32% of patients in the older group and in 51% of patients in the control group ($p < 0.0001$). Both thiopurines and anti-TNF agents were prescribed significantly more often in the control group (Table 2). Moreover, no differences were observed in the proportion of patients starting preventive treatment with thiopurines or anti-TNF agents when long-lasting and elderly-onset CD groups were compared (Supporting Information S1: Table 2a).

TABLE 2 | Main characteristics at index surgery in older and control study groups.

	Older group ($n = 535$)	Control group ($n = 3454$)	p
Age at surgery	67.6 ± 10.2	37.7 ± 13.6	< 0.0001
Indication of surgery			
Intestinal stricture	246 (46)	1290 (37)	< 0.0001
Penetrating complications	103 (19)	1020 (29)	< 0.0001
Refractoriness	94 (17.5)	654 (19)	0.45
Other	92 (17)	490 (14)	0.02
Time since CD diagnosis, *months*	114.6 ± 128.7	93.2 ± 97.2	< 0.0001
Prevention for POR			
Thiopurines	109 (20)	1104 (32)	< 0.0001
Anti-TNF agents	66 (12)	648 (19)	< 0.0001
Surgical POR	94 (17.5)	627 (18)	0.74
Median follow-up from index surgery, *months*	65.5 ± 56.1	80.9 ± 56.0	< 0.0001
Mortality rate	2	1	0.049

3.3 | Surgical Postoperative Recurrence

Median follow-up after the index surgery was significantly shorter in the older group (65.5 ± 56.1 vs. 80.9 ± 56 months; $p < 0.0001$). At the end of follow-up, a total of 94 patients (17.5%) in the older group and 627 (18.2%) in the control group developed surgical POR ($p = 0.74$), leading to an incidence of surgical recurrence of 0.002 patients-years in both groups. Figure 2 shows the rates of surgical POR-free survival. Despite the differences regarding POR prevention, the cumulative risk of surgical POR was 3.2%, 5.3% and 10.1% in the older group and 3.6%, 6.6% and 14.2% in the control group at 3, 5 and 10 years, respectively (log-rank $p = 0.093$).

In the Cox regression analysis, only preventive treatment with thiopurines was associated with a lower risk of surgical POR in the whole cohort (Table 3).

4 | Discussion

It has been reported that, despite the evidence of a milder phenotype in elderly-onset CD [22, 24], the rates of surgery and hospitalization in these patients are similar to those of adult-onset CD [21–23]. Therefore, the notion of a 'less aggressive phenotype' remains uncertain, and further studies are needed to clarify whether these observed differences reflect disease biology or treatment patterns. Furthermore, relying only on reoperation to define surgical POR in older patients may introduce bias. Frailty, comorbidities, or patient preference could reduce the likelihood of undergoing a second resection, potentially underestimating the 'true' POR rate in this group. Conversely, the shorter time from diagnosis to surgery observed in elderly-onset CD may reflect a lower surgical threshold, which could lead to an overestimation of POR when using surgical endpoints alone.

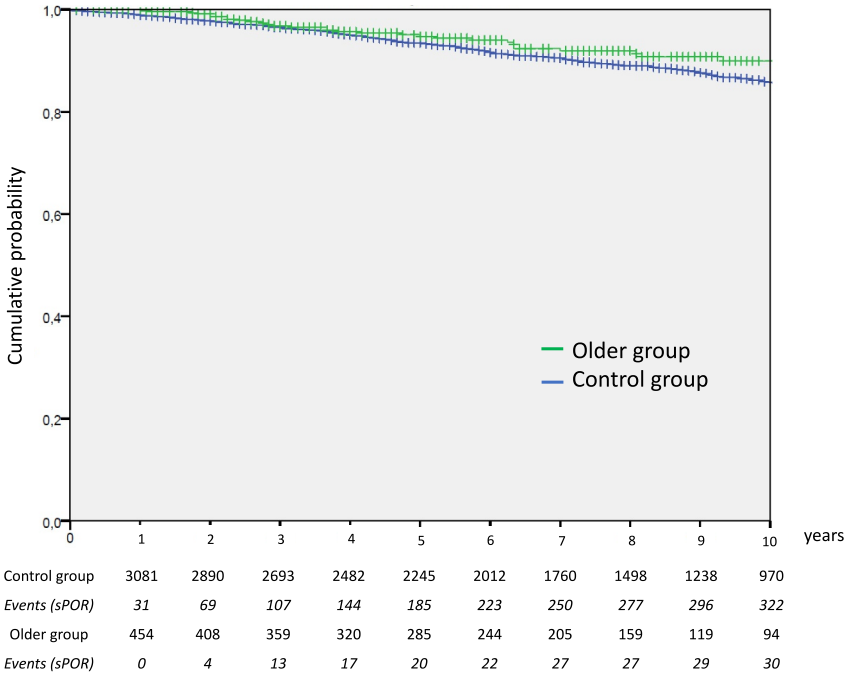

FIGURE 2 | Cumulative probability of remaining free of surgical POR.

TABLE 3 | Risk factors for surgical postoperative recurrence.

	Multivariate analysis	
	HR (95% CI)	*p*-value
Female gender	0.85 (0.69–1.05)	0.127
Penetrating behaviour	4.44 (0.62–31.86)	0.138
Inflammatory disease behaviour	4,82 (0.67–35.27)	0.115
Stricturing disease behaviour	4.17 (0.58–29.94)	0.155
Perianal disease prior to surgery	0.98 (0.78–1.24)	0.9
Surgery for intestinal stricture	1.10 (0.85–1.42)	0.45
Surgery for penetrating complication	0.97 (0.88–1.06)	0.54
Anti-TNF exposure prior to surgery	1.04 (0.84–1.29)	0.68
Prevention with immunomodulators	0.78 (0.62–0.98)	0.032
Prevention with anti-TNF	1.04 (0.79–1.37)	0.77
Older group (vs. Controls)	1.07 (0.14–8.25)	0.94
Elderly long-lasting CD (vs. Controls)	0.62 (0.08–4.45)	0.64
Elderly-onset CD (vs. Controls)	0.68 (0.08–5.56)	0.72

In the present study, which focussed on patients with CD undergoing a first intestinal resection, we observed a different disease pattern and location in older patients compared with controls, suggesting that additional factors, such as a higher risk for severe drug-related adverse effects, may play a role in the therapeutic approach in older patients. In this scenario, surgery represents a cornerstone in CD management for patients who are unable to tolerate medical treatment or for whom such treatments failed.

In addition, life expectancy has increased overall, and patients diagnosed with CD at a young age are also reaching older age and physicians are therefore increasingly facing the challenge of managing older CD patients with elderly-onset and long-lasting disease. Data regarding surgery in elderly-onset CD patients compared with long-lasting CD patients are not yet available. In our study, we observed differences in management regarding exposure to immunomodulators and biological agents prior to surgery, with a higher prescription of these therapies in long-term CD patients compared with elderly-onset CD patients.

As expected, and as previously reported [28], the time from diagnosis of CD to surgery was shorter in the older group than for controls due to an earlier first resection in elderly-onset CD patients. A shorter time between disease onset and first surgery is presumed to be related to the need for excluding malignancy [29, 30].

Regarding postoperative management, Spanish guidelines for the management of postoperative CD published in 2017 recommended preventive treatment for POR with thiopurines or anti-TNF in high-risk patients [30]. In our cohort, only half of patients in the control group started preventive treatment for POR and this figure was significantly lower in the older group; although this may have been due to safety concerns regarding older patients, the higher proportion of surgery for intestinal stenosis among older patients may also have played a role in decision-making. Conversely, the proportion of patients starting preventive treatment for POR was similar in patients with long-lasting and elderly-onset CD, suggesting that age rather than disease duration is the main decision-making driver in this population. Of note, despite a different strategy for POR prevention, no differences in the surgical POR rates were observed between older patients and controls, with 10%–15% likelihood of a second intestinal resection within 10 years. Of course, our data highlight the need for a similar preventive monitoring postoperative strategy in older and younger patients.

Age is not considered a risk factor of POR [4, 31], but the impact of older age has not been specifically addressed in the postoperative setting and no specific data on the risk of endoscopic POR in the elderly are available from randomized controlled trials (RCT). In fact, in the largest RCT published to date assessing the efficacy of biological agents and thiopurines in the postoperative setting, the median age of patients was 36 years [32]. However, a recent study evaluated the accuracy of the criteria defining a high risk of endoscopic POR as defined by different IBD societies to predict the incidence of endoscopic POR in a retrospective cohort [33] and found that older age at diagnosis (as defined by the Montreal classification group A3 -> 40 years) was significantly associated with a 3-fold increase in the odds of endoscopic POR [33].

Controversial data are available regarding clinical POR. The first study assessing clinical POR in older adults showed that the risk of clinical recurrence after intestinal resection was five times less in patients over the age of 50 years [34]. Similarly, another study performed in the pre-biological era assessed clinical recurrence after bowel resection in 98 patients with CD over 40 years of age compared with 347 younger adults, and found that recurrence was less common among the older patients; however, when clinical POR did occur, time to recurrence was significantly shorter in older patients [29]. A recent but small and retrospective Italian study showed similar rates of clinical POR between patients over and below 65 years of age [35].

Data are also scarce and controversial regarding surgical POR. In an older study of surgical POR in a cohort of 101 patients, age was not a risk factor for surgical POR [36]. Conversely, O'Keefe et al. showed a lower surgical POR rate in the elderly [37] and a more recent Italian study in 1050 CD patients grouped into four age groups showed that age at surgery was an independent risk factor for surgical POR, with a greater risk for younger patients [38].

The main strengths of the present study are its sample size, since it is the largest published to date with the aim of assessing surgical POR in older patients and uses an objective, strong endpoint such as surgical POR. Moreover, we provide data for the first time comparing the postoperative management of CD in elderly-onset long-lasting disease. Nonetheless, we are aware of several limitations. Firstly, due to its retrospective design, no data on clinical or endoscopic POR were available. In fact, we focussed on surgical POR in order to minimize the bias related to the unavailability of a standardized definition of clinical POR. Secondly, no data on comorbidities were available. We are aware that comorbidities are one of the main drivers for therapeutic decision-making in older adults and that conclusions must therefore be drawn with caution. Third, postoperative management was heterogeneous and relied on the discretion of the treating physician, introducing an important bias that might impact surgical POR. Finally, at the time data were extracted from the registry, the use of ustekinumab and vedolizumab in this cohort was negligible. We are aware that these drugs are increasingly used in older patients instead of anti-TNF agents, and this might change the long-term outcomes in the postoperative setting.

In conclusion, older patients with CD are less often preventively treated with immunomodulators or biologicals after a first intestinal resection, regardless of the duration of the disease. However, they develop surgical POR as often as younger adult patients, with a cumulative probability of surgical POR of 10% 10 years after the index surgery.

Affiliations

[1]Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain | [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III, Madrid, Spain | [3]Department of Gastroenterology, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain | [4]Department of Gastroenterology, Hospital Universitari i Politècnic La Fe, Valencia, Spain | [5]Department of Gastroenterology, Hospital Universitario Reina Sofia, IMIBIC, Universidad de Córdoba (UCO), Córdoba, Spain | [6]Department of Gastroenterology, Hospital Universitario Central de Asturias, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain | [7]Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Madrid, Spain | [8]Department of Gastroenterology, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain | [9]Department of Gastroenterology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain [10]Department of Gastroenterology, Hospital Álvaro Cunqueiro, Instituto de Investigación Sanitaria Galicia Sur, Vigo, Spain | [11]Department of Gastroenterology, Hospital Universitario Marqués de Valdecilla, Instituto de Investigación IDIVAL, Santander, Spain | [12]Department of Gastroenterology, Complexo Hospitalario Universitario de Pontevedra, Pontevedra, Spain | [13]Department of Gastroenterology, Hospital Clínico Universitario de Valencia, Valencia, Spain | [14]Department of Gastroenterology, Hospital Clínico San Carlos, Madrid, Spain | [15]Department of Gastroenterology, Hospital Universitario La Paz, Madrid, Spain | [16]Department of Gastroenterology, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain | [17]Department of Gastroenterology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain | [18]Department of Gastroenterology, Hospital Universitario Miguel Servet, Zaragoza, Spain | [19]Department of Gastroenterology, Hospital General Universitario de Alicante, ISABIAL, Alicante, Spain | [20]Department of Gastroenterology, Hospital Universitari Parc Taulí de Sabadell, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain [21]Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | [22]Department of Gastroenterology, Hospital Universitario Río Hortega, Valladolid, Spain | [23]Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Madrid, Spain | [24]Department of Gastroenterology, Hospital Universitario de Burgos, Burgos, Spain | [25]Department of Gastroenterology, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain | [26]Department of Gastroenterology, Biodonostia Health Research Institute–Donostia University Hospital, Universidad del País Vasco (UPV/EHU), San Sebastián (Donostia), Spain | [27]Department of Gastroenterology, Hospital Universitari Mútua de Terrassa, Terrassa, Spain | [28]Department of Gastroenterology, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain | [29]Department of Gastroenterology, Hospital Universitario de Cabueñes, Gijón, Spain [30]Department of Gastroenterology, Complejo Asistencial Universitario de León, León, Spain | [31]Department of Gastroenterology, Hospital Universitario de Cruces, Barakaldo, Spain | [32]Department of Gastroenterology, Hospital Universitario de Fuenlabrada, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Fuenlabrada, Spain | [33]Department of Gastroenterology, Hospital Clínico Univers itario de Santiago, Santiago de Compostela, Spain | [34]Department of Gastroenterology, Hospital Universitario de Salamanca, Salamanca, Spain | [35]Department of Gastroenterology, Hospital del Mar, Barcelona, Spain | [36]Department of Gastroenterology, Hospital Moisès Broggi, Sant Joan Despí, Spain | [37]Department of Gastroenterology, Hospital Universitario de Galdakao, Galdakao, Spain | [38]Department of Gastroenterology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain | [39]Department of Gastroenterology, Hospital General Universitario de Elche, Elche, Spain | [40]Department of Gastroenterology, Hospital de Manises, Manises, Spain | [41]Department of Gastroenterology, Complexo Hospitalario Universitario de Ourense, Ourense, Spain | [42]Department of Gastroenterology, Consorci Sanitari de Terrassa, Terrassa, Spain | [43]Department of Gastroenterology, Hospital Universitario de Navarra, Pamplona, Spain | [44]Department of Gastroenterology, Hospital de Girona Doctor Josep Trueta, Girona, Spain [45]Department of Gastroenterology, Hospital Universitario 12 de Octubre, Madrid, Spain | [46]Department of Gastroenterology, Hospital Son Llàtzer, Palma de Mallorca, Balearic Islands, Spain | [47]Department of Gastroenterology, Hospital Virgen de la Victoria, Málaga, Spain | [48]Department of Gastroenterology, Althaia, Xarxa Assistencial Universitària de Manresa, Manresa, Spain | [49]Instituto de Investigacion Sanitaria Gregorio Maranon, Madrid, Spain | [50]Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Universidad Complutense de Madrid, Madrid, Spain | [51]Department of Gastroenterology, Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Spain | [52]Department of Gastroenterology, Hospital Universitario de Torrejón, Torrejón de Ardoz, Spain | [53]Department of Gastroenterology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain | [54]Department of Gastroenterology, Hospital Universitari Son Espases, Palma de Mallorca, Spain | [55]Department of Gastroenterology, Hospital General de Granollers, Granollers, Spain | [56]Department of Gastroenterology, Hospital San Jorge, Huesca, Spain | [57]Department of Gastroenterology, Complejo Hospitalario La Mancha Centro, Alcázar de San Juan, Spain | [58]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain | [59]Department of Gastroenterology, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain | [60]Department of Gastroenterology, Hospital Universitario Joan XXIII, Tarragona, Spain | [61]Department of Gastroenterology, Hospital General Universitario de Castellón, Castellón de la Plana, Spain | [62]Department of Gastroenterology, Hospital Universitario Infanta Leonor, Madrid, Spain | [63]Department of Gastroenterology, Complejo Asistencial de Zamora, Zamora, Spain | [64]Department of Gastroenterology, Complejo Asistencial Universitario de Palencia, Palencia, Spain | [65]Department of Gastroenterology, Hospital Virgen de la Luz, Cuenca, Spain | [66]Department of Gastroenterology, Hospital Universitario de Basurto, Bilbao, Spain | [67]Department of Gastroenterology, Hospital Universitario Virgen Macarena, Universidad de Sevilla, Seville, Spain | [68]Department of

Gastroenterology, Complejo Asistencial de Segovia, Segovia, Spain [69]Department of Gastroenterology, Hospital de Viladecans, Viladecans, Spain | [70]Department of Gastroenterology, Hospital Royo Villanova, Zaragoza, Spain | [71]Department of Gastroenterology, Complejo Hospitalario de Jaén, Jaén, Spain | [72]Department of Gastroenterology, Hospital San Pedro, Logroño, Spain | [73]Department of Gastroenterology, Hospital Santa Bárbara, Soria, Spain | [74]Department of Gastroenterology, Hospital Santos Reyes, Aranda de Duero, Spain | [75]Department of Gastroenterology, Hospital Vega Baja, Orihuela, Spain

Author Contributions

MM and ED designed the study, performed the statistical analysis, evaluated the results and drafted the article. The remaining authors collected data and critically reviewed and approved the article.

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Conflicts of Interest

MM has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Gilead, Janssen, MSD, Pfizer, Faes, Takeda and Tillots; MC has served as a speaker for Takeda, Janssen, Faes Farma and MSD; ER has received support for congress and conference attendance, speaker fees, research support or consulting fees from MSD, Abbvie, Ferring, Janssen, Otsuka, Pfizer, Takeda, Galapagos, Kern Pharma and Fresenius Kabi; PN has served as a speaker, consultant and advisory board member or has received research funding from MSD, Abbvie, Janssen, Takeda, Roche, Sandoz, Ferring, Adacyte, Faes Farma, Kern Pharma, Pfizer, Shire Pharmaceuticals, Vifor Pharma, Chiesi and Tillots; EI has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Janssen, Takeda, Pfizer, Ferring, Faes Farma, Dr. Falk Pharma and Chiesi; SR has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Adacyte Therapeutics, Janssen, Kern Pharma, MSD, Pfizer,Takeda, Tillots, and Ferring; MC has served as a speaker, consultant and advisory member for or has received research funding from MSD, Abbvie, Takeda, Jannsen, Pfizer, Lilly, Mylan, Kern Pharma, Ferring, Shire Pharmaceuticals, Tillots, Dr. Falk Pharma, Chiesi and Gebro Pharma; VH has served as a consultant or speaker and has received travel support or research funding from Abbvie, Ferring, Dr Falk Pharma, Tillots Pharma, Pfizer, Takeda, Janssen, Kern Pharma, Adacyte, Sandoz, Biogen, Fresenius-Kabi, FAES farma and Galapagos; MR has served as a speaker or advisory member for TaKeda, Janssen, Galapagos, Ferring and Pfizer; SGL has served as a speaker, consultant or has received research or educational funding or advisory fees from Abbvie, Janssen, MSD, Pfizer and Takeda; AGC has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Galapagos, Pfizer, Sandoz, Fresenius, Lilly, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, and Adacyte; XC has served as speaker, consultant and advisory member for or has received research funding from MSD, Abvie, Pfizer, Kern Pharma, Takeda, Janssen, Sandoz, Galapagos, Lilly, Shire Pharmaceuticals and Vifor Pharma; JPG has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma; JPC has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Biogen, Dr. Falk, Janssen, Faes, Takeda and Tillots; ME has received support for conference attendance and research from Abbvie, Ferring, Janssen, Pfizer, Takeda, Vifor Pharma and Tillots; MS has served as a speaker and advisory member and has received research funding from Abbvie, Pfizer, MSD, Takeda, Janssen, Ferring, Sandoz, Faes Farma, Chiesi and Galapagos; FB has been a speaker, consultant and advisory member or has received research funding from MSD, Abbvie, Takeda, Janssen, Pfizer, Biogen, Amgen, Galapagos, Ferring, Faes Farma, Tillotts Pharma, Chiesi and Vifor Pharma; MBA has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, GALAPAGOS, Pfizer, Sandoz, Biogen, Fresenius, Lilly, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, Gebro Pharma, Adacyte and Vifor Pharma; OGB has served as a speaker for or has received research funding from AbbVie, Janssen, Takeda, Pfizer, Ferring, Tillots Pharma and Dr. Falk Pharma; IR-L has received financial support for travelling and educational activities from or has served as an advisory board member for Abvie, Adacyte, Celltrion, Chiesi, Danone, Ferring. 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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supporting Information S1: ueg270150-sup-0001-suppl-data.docx.