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ORIGINAL RESEARCH

Advanced Therapies in Elderly Patients With Inflammatory Bowel Disease: A Comparative Retrospective Cohort Study in Taiwan

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Purpose: Inflammatory Bowel Disease (IBD) predominantly affects younger individuals, but emerging data indicates a shift toward older populations. Elderly-onset IBD (diagnosed at 60 years or older) differs from younger-onset IBD, presenting with atypical symptoms and higher risks of infections and malignancies. However, drug persistence is underexplored in the elderly IBD group, warranting further investigation to optimize treatment strategies for this demographic.

Patients and Methods: This retrospective cohort study included IBD patients receiving advanced therapies at the Chang Gung IBD Center from October 2017 to September 2023. Patients were stratified into two groups: elderly-onset (≥60 years) and control (<60 years). We compared one-year persistence of advanced therapies, opportunistic infections, IBD-related admissions, complications, surgeries, and acute flare-ups between the groups. Specifically, we analyzed the one-year persistence of various advanced therapies within the elderly-onset cohort.

Results: The study included 511 IBD patients, 107 of whom were elderly-onset. Elderly-onset patients had a higher body mass index, a higher proportion of ulcerative colitis, fewer smokers, and lower levels of white blood cells, hemoglobin, and albumin. Differences were noted in Montreal classifications and a higher use of Vedolizumab. Clinical outcomes, including steroid-free remission rates, one-year therapy persistence, infections, complications, surgeries, and flare-ups, were comparable between groups. In Crohn's disease (CD), Infliximab and Ustekinumab exhibited higher one-year persistence. Predictors of one-year therapy persistence included Montreal L1 (OR: 6.722; 95% CI: 1.296–34.852; P=0.023), Ustekinumab use (OR: 5.672; 95% CI: 1.138–28.267; P=0.034), and hemoglobin level (OR: 1.612; 95% CI: 1.210–2.147; P=0.001) with an optimal cutoff of 11.65 g/dL.

Conclusion: Elderly-onset IBD patients display unique clinical characteristics and therapy persistence, particularly in CD, highlighting the necessity for customized therapeutic strategies.

Keywords: elderly-onset inflammatory bowel disease, advanced therapies, drug persistence, clinical outcomes

Introduction

Recent epidemiological studies have highlighted the evolving global burden of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). While IBD was historically considered more prevalent in Western countries, increasing evidence suggests a rising incidence in Asian nations.[1,2] This shift aligns with the four epidemiological stages of IBD evolution, reflecting changing environmental and lifestyle factors.[2] Moreover, recent findings indicate that IBD in Asian populations may exhibit distinct demographic and phenotypic characteristics

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compared to Western cohorts.[3] Additionally, the increasing diagnosis of IBD in elderly populations underscores its expanding global impact.[4] As populations age, the prevalence of elderly IBD patients has surged rapidly.[2,4] With aging populations, the prevalence of elderly IBD patients has increased, with approximately 25–35% now aged 60 or older.[2,4–7] IBD diagnosed at this age is categorized as elderly-onset IBD.[6] Notably, 10–20% of newly diagnosed IBD cases occur in this demographic, and these figures are anticipated to rise with the ongoing aging of societies.[6–12] In recent decades, advanced therapies, including biologic agents and small molecule therapies, have revolutionized the treatment landscape for IBD and are now integral to managing IBD.[13] The effectiveness and persistence of these advanced therapies are crucial, given the chronic nature of IBD which necessitates long-term management to alleviate symptoms and prevent disease exacerbation.[14,15] However, studies focusing on drug persistence in the elderly, remain scarce. Elevated discontinuation rates of anti-TNF-α therapies have been documented in the elderly population, primarily due to lower clinical responses and increased infection-related complications, which are common reasons for therapy cessation.[16–21] Additionally, older age has been identified as an independent factor influencing drug discontinuation.[16,17,22] Despite these challenges, few studies have specifically investigated drug persistence and predictive factors for persistence of other advanced therapies in the elderly-onset population.

Our study aims to compare the 1-year persistence of advanced therapies between elderly-onset and control groups in both CD and UC. Additionally, we seek to identify independent predictive factors for 1-year drug persistence specifically within the elderly-onset group.

Materials and Methods

Study Population and Endpoints

This retrospective cohort study included all IBD patients who received advanced therapies and regularly followed up in the Chang Gung IBD center between October 2017 and September 2023. After enrollment, all patients were prospectively followed until either drug discontinuation or January 2024. Patients who did not receive advanced therapies or were pregnant were excluded from the study. The study population was divided into two groups: the control group (patients younger than 60 years) and the elderly group (patients aged 60 years or older), in accordance with the European Crohn's and Colitis Organization (ECCO) Topical Review.[6] Due to the national health insurance regulations, which limit the use of advanced therapies to one year, the primary objective of this study was to compare the one-year drug persistence between the control and elderly groups. Additionally, we sought to identify baseline predictors of one-year drug persistence within the elderly subgroup.

Data Collection and Definition

Patient data were collected from medical records, including the date of diagnosis, age, gender, body mass index (BMI), and disease location/extent in both CD and UC. We also recorded laboratory results at the start of biologic therapy, prior biologic agent use (adalimumab, golimumab, infliximab, vedolizumab, ustekinumab, tofacitinib), or biologic-naïve status, as well as current biologic therapy (adalimumab, infliximab, vedolizumab, ustekinumab, tofacitinib), along with the dates of the initial and final doses. Concomitant use of 5-ASA, corticosteroids, or thiopurines was noted. Corticosteroid-free remission was defined as corticosteroid discontinuation for at least 12 weeks prior to the 52nd week of therapy.[23] Additional data collected included dose escalation history, drug administration intervals, IBD-related hospital admissions, opportunistic infections, IBD complications (eg, strictures, perforations, abscesses, fistulas), IBD-related surgeries, and the number of acute flare-ups. Opportunistic infections were defined to include Cytomegalovirus (CMV), *Clostridioides difficile* (*C. difficile*), *Clostridium innocuum* (*C. innocuum*), and Herpes Simplex virus (HSV) infections.[24] CMV infection was identified by the presence of typical viral inclusion bodies on colonic mucosal biopsy.[24,25] *C. difficile* infection was diagnosed via positive *C. difficile* toxin gene screening.[24] *C. innocuum* infection was identified by stool culture, and HSV infection was defined by a positive serum IgM or DNA test.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD), depending on their distribution, and compared using the Independent Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for non-normally distributed data. Categorical variables were presented as frequencies and percentages, with comparisons made using the Chi-square test. Fisher's exact test was applied when more than 20% of the expected frequencies in the statistical cells were less than five. Drug persistence was assessed using Kaplan–Meier analysis and compared with the Log rank test, with a log-rank p-value < 0.05 considered statistically significant. Univariate and multivariate logistic regression analyses were employed to identify baseline predictors of drug persistence through the 52nd week in the overall cohort, as well as in the elderly subgroup. Variables with a p-value ≤ 0.05 in univariate analysis were included in the multivariate analyses. Odds ratios (OR) were calculated with 95% confidence intervals (CI). Missing data were addressed using appropriate statistical methods based on available data analysis techniques. All statistical analyses were performed using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA).

Result

Patient Characteristics and Clinical Outcomes

This study included 511 patients with IBD, of whom 107 were classified as elderly-onset, while the remaining patients formed the control group (Table 1). The elderly-onset group had a higher BMI, fewer cases of CD, fewer smokers, and lower levels of white blood cells, hemoglobin, and albumin. Additionally, the elderly-onset group showed fewer cases of

Table 1 Baseline Characteristics and Clinical Outcomes Between Elderly and Control Cohorts

	Overall (n = 511)	**Elderly Group (n= 107)**	**Control Group (n = 404)**	**P-value**
Baseline				
Age (mean ± SD years)	44.20 ± 16.12	69.15 ± 5.69	37.96 ± 10.73	<0.001*
Gender (male)	347 (67.91%)	65 (60.75%)	282 (69.80%)	0.074
Body mass index (mean ± SD, kg/m^2)	19.72 ± 9.04	20.36 ± 8.19	19.55 ± 9.26	0.013*
Inflammatory bowel disease (Crohn's disease)	301 (58.90%)	52 (48.60%)	249 (61.63%)	0.015*
Smoking	49 (9.59%)	4 (3.74%)	45 (11.14%)	0.021*
Laboratory test				
White blood cell (1000/uL)	8.54 ± 3.55	7.48 ± 3.04	8.83 ± 3.63	<0.001*
Hemoglobin (g/dL)	12.73 ± 7.44	11.63 ± 2.03	12.46 ± 2.25	<0.001*
C-Reactive Protein (mg/L)	13.09 ± 26.43	8.16 ± 12.39	14.40 ± 28.91	0.528
Albumin (g/dL)	3.92 ± 0.64	3.69 ± 0.65	3.98 ± 0.62	<0.001*
Montreal classification				
Crohn's disease				
L1	119 (30.83%)	23 (44.23%)	96 (38.55%)	0.622
L2	34 (8.81%)	8 (15.38%)	26 (10.44%)	0.701
L3	137 (35.49%)	19 (36.54%)	118 (47.39%)	0.017*
L4	96 (24.87%)	22 (42.31%)	74 (29.72%)	0.597
B1	160 (44.94%)	28 (53.85%)	132 (53.01%)	0.197
B2	128 (35.96%)	18 (34.62%)	110 (44.18%)	0.027*
B3	56 (15.73%)	15 (28.85%)	41 (16.47%)	0.254
Peri-anal disease	12 (3.37%)	0	12 (4.82%)	0.080
Ulcerative colitis				
E1	20 (9.52%)	8 (14.55%)	12 (7.74%)	0.046*
E2	76 (36.19%)	15 (27.27%)	61 (39.35%)	0.780
E3	114 (54.29%)	32 (58.18%)	82 (52.90%)	0.034*
Biologic-naïve	243 (47.55%)	51 (47.66%)	192 (47.52%)	0.980

(*Continued*)

Table 1 (Continued).

	Overall (n = 511)	Elderly Group (n= 107)	Control Group (n = 404)	P-value
Biologic-experienced				
Adalimumab	133 (34.28%)	24 (22.43%)	109 (26.98%)	0.340
Golimumab	1 (0.26%)	1 (0.93%)	0	0.209
Infliximab	41 (10.57%)	9 (8.41%)	32 (7.92%)	0.868
Tofacitinib	7 (1.80%)	1 (0.93%)	6 (1.49%)	1.000
Ustekinumab	56 (14.43%)	7 (6.54%)	49 (12.13%)	0.100
Vedolizumab	150 (38.66%)	41 (38.32%)	109 (26.98%)	0.022*
Current biological agents use				
Adalimumab	106 (20.74%)	17 (15.89%)	89 (22.03%)	0.164
Infliximab	51 (9.98%)	9 (8.41%)	42 (10.40%)	0.542
Tofacitinib	12 (2.35%)	2 (1.87%)	10 (2.48%)	1.000
Ustekinumab	149 (29.16%)	29 (27.10%)	120 (29.70%)	0.599
Vedolizumab	193 (37.77%)	50 (46.73%)	143 (35.40%)	0.032*
Combine with biologic therapy				
5-ASA	321 (62.82%)	73 (68.22%)	247 (61.14%)	0.187
Steroid	294 (57.53%)	66 (61.68%)	228 (56.44%)	0.329
Immunosuppressants	139 (27.20%)	28 (26.17%)	112 (27.72%)	0.749
Outcome				
Dose escalation	72 (14.09%)	18 (16.82%)	54 (13.37%)	0.333
Use advanced therapy until 1 year	395 (77.30%)	79 (73.83%)	316 (78.22%)	0.336
Steroid-free remission at 1 year	361 (70.65%)	78 (72.90%)	283 (70.05%)	0.565
Persistence (weeks)	50.56 ± 29.60	50.32 ± 25.75	50.61 ± 30.56	0.931
IBD related admission (times/person/year)	0.23	0.23	0.23	
Reason of IBD related admission				
Opportunistic infection	74 (14.48%)	21 (19.63%)	53 (13.12%)	0.134
Cytomegalovirus	16 (3.13%)	7 (6.54%)	9 (2.23%)	0.053
Clostridioides difficile	33 (6.46%)	8 (7.48%)	25 (6.19%)	0.694
Clostridium innocuum	24 (4.70%)	6 (5.61%)	18 (4.46%)	0.616
Herpes Simplex Virus	1 (0.20%)	0	1 (0.25%)	1.000
IBD related complications	11 (2.15%)	2 (1.87%)	9 (2.23%)	1.000
IBD related surgeries	25 (4.89%)	3 (2.80%)	22 (5.45%)	0.592
Acute flare-up	85 (16.63%)	15 (14.02%)	70 (17.33%)	0.423

Notes:. *P < 0.05. Continuous variables were presented as mean ± standard deviation (SD), depending on their distribution, and compared using the Independent Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for non-normally distributed data. Categorical variables were presented as frequencies and percentages, with comparisons made using the Chi-square test. Fisher's exact test was applied when more than 20% of the expected frequencies in the statistical cells were less than five.IBD complications: strictures, perforations, abscesses, fistulas…etc.
Abbreviations: 5-ASA, 5-Aminosalicylic Acid; IBD, inflammatory bowel disease.

ileocolonic involvement and strictures in CD, but a higher incidence of UC with proctitis and extensive colitis. This group also had a higher proportion of patients using vedolizumab. Despite these differences, there were no significant disparities between the two groups in terms of steroid-free remission at 52 weeks, 1-year drug persistence, opportunistic infections, IBD-related complications, surgeries, or acute flare-ups.

The Persistence of Advanced Therapies

We first compared the 1-year drug persistence of advanced therapies between the elderly-onset and control groups for both CD and UC (Figure 1). Among the 301 CD patients, 52 were in the elderly-onset group, while the remaining 249 were in the control group. A total of 245 CD patients (81.34%) used advanced therapies for at least one year, including 42 from the elderly-onset group (42/52, 80.77%) and 203 from the control group (203/249, 81.53%). Kaplan–Meier analysis showed no significant difference in 1-year drug persistence between the elderly-onset and control groups for CD

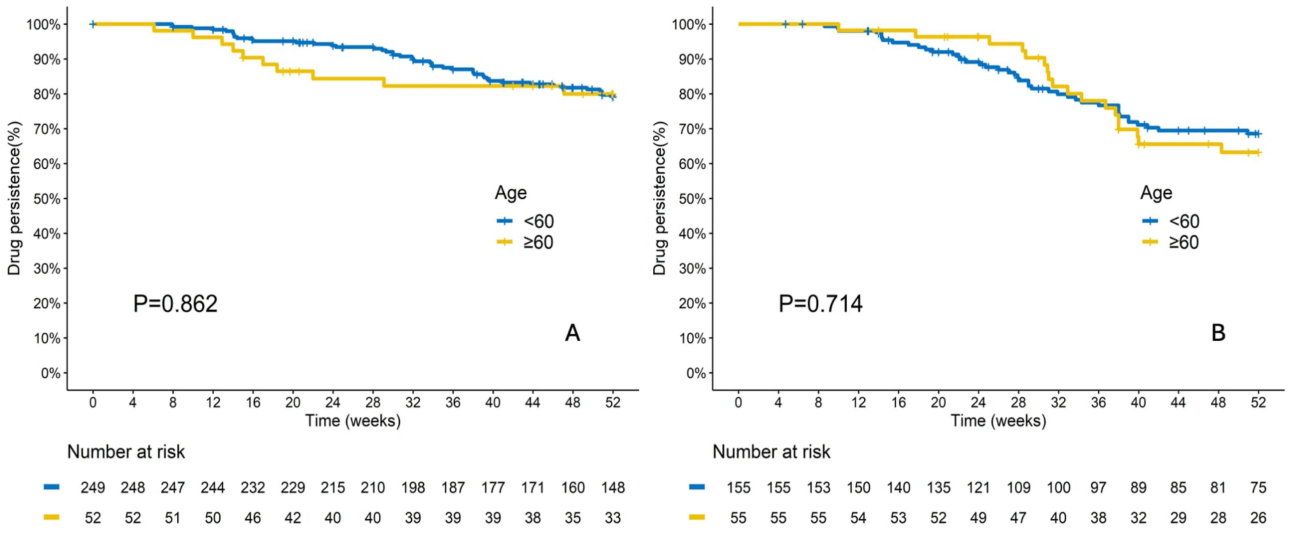

Figure 1 Kaplan-Meier curves comparing 1-year drug persistence between elderly-onset (≥60 years) and younger (<60 years) patients with Crohn's disease (CD, (**A**) and ulcerative colitis (UC, (**B**) show no significant differences between age groups (P = 0.862 for CD, P = 0.714 for UC).

(Log-rank P = 0.862, Figure 1A). In the UC cohort, 150 patients (71.43%) used advanced therapies for at least one year, including 37 patients from the elderly-onset group (37/55, 67.27%) and 113 from the control group (113/155, 72.90%). Kaplan–Meier analysis again showed no significant difference in 1-year drug persistence between the two groups for UC (Log-rank P = 0.714, Figure 1B).

Next, we assessed drug persistence for each advanced therapy within the elderly-onset group (Figure 2). In the CD subgroup, 42 patients receiving advanced therapies for at least one year (42/52, 80.77%). Among the 7 patients treated with adalimumab, 5 continued therapy for at least one year (5/7, 71.43%). All 6 patients treated with infliximab continued therapy for at least one year (6/6, 100%). Among the 20 patients treated with ustekinumab, 19 persisted for at least one year (19/20, 95.00%). Among the 19 patients treated with vedolizumab, 12 maintained therapy for at least one year (12/19, 63.16%). Kaplan–Meier analysis revealed a significant difference in drug persistence among the different therapies for CD (Log-rank P = 0.036, Figure 2A). In the UC subgroup, 37 patients persisted with advanced therapies for at least one year (37/55, 67.27%). Of the 10 patients treated with adalimumab, only 4 persisted for one year (4/10, 40.00%). Among the 3 patients who received infliximab,2 continued treatment for at least one year (2/3, 66.67%).

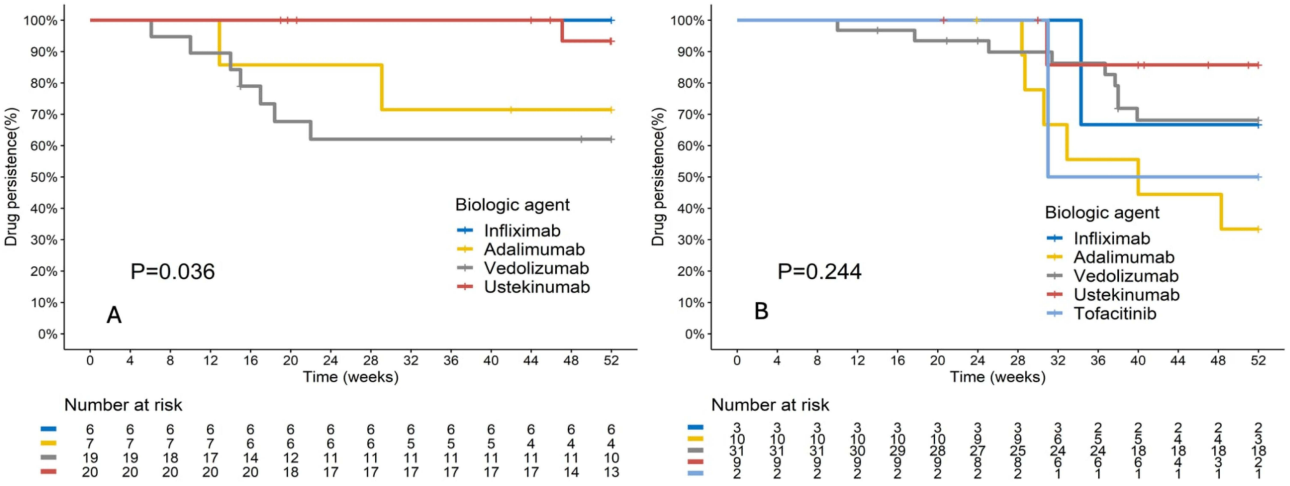

Figure 2 Kaplan-Meier curves depicting 1-year drug persistence of advanced therapies in elderly-onset patients with Crohn's disease (CD, (**A**) and ulcerative colitis (UC, (**B**) demonstrate a significant difference among biologic agents in CD (P = 0.036), while no significant difference is observed in UC (P = 0.244).

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Two patients were treated with tofacitinib, with one persisting for at least one year (1/2, 50.00%). Of the 9 patients treated with ustekinumab, and 8 patients used it for at least one year (8/9, 88.89%). Among the 31 patients treated with vedolizumab, 22 persisted for one year (22/31, 70.97%). However, Kaplan–Meier analysis showed no significant difference in drug persistence among the different therapies for UC (Log-rank P = 0.244, Figure 2B).

Predictive Factors for the Persistence of Advanced Therapies in the Elderly-Onset Group

We conducted logistic regression to identify baseline characteristics associated with drug persistence in the elderly-onset group (Table 2). Three independent factors significantly influenced drug persistence: Montreal classification L1 (OR: 6.722;

Table 2 Logistic Regression Analysis of 1-year Persistence in Elderly-Onset IBD Patients

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Gender (male)	0.816	0.340–1.959	0.650			
Body mass index (mean ± SD, kg/m^2)	1.005	0.954–1.059	0.850			
Inflammatory bowel disease (Crohn's disease)	2.043	0.839–4.978	0.116			
Smoking	0.977	0.255–3.740	0.973			
Montreal Classification						
L1	4.707	1.027–21.572	0.046*	6.722	1.296–34.852	0.023*
L2	1.068	0.203–5.629	0.938			
L3	0.722	0.245–2.129	0.555			
L4	1.770	0.543–5.773	0.343			
B1	1.415	0.506–3.956	0.508			
B2	1.953	0.520–7.333	0.321			
B3	1.493	0.388–5.734	0.560			
Peri-anal disease	0					
E1	2.625	0.308–22.344	0.377			
E2	1.493	0.388–5.734	0.560			
E3	0.295	0.119–0.732	0.008*			
Biologic-naïve	0.489	0.203–1.178	0.111			
Biologic-experienced						
Adalimumab	5.018	1.097–22.942	0.038*			
Golimumab	0	0	1.000			
Infliximab	3.042	0.363–25.487	0.305			
Tofacitinib	0	0	1.000			
Ustekinumab	0	0	0.999			
Vedolizumab	1.162	0.475–2.846	0.742			
Current biologic agent						
Adalimumab	0.321	0.110–0.941	0.038*			
Infliximab	3.042	0.363–25.487	0.305			
Tofacitinib	0.346	0.021–5.727	0.459			
Ustekinumab	6.750	1.489–30.601	0.013*	5.672	1.138–28.267	0.034*
Vedolizumab	0.567	0.237–1.354	0.201			
Laboratory test						
White blood cell (1000/uL)	1.108	0.940–1.308	0.221			
Hemoglobin (g/dL)	1.506	1.172–1.936	0.001*	1.612	1.210–2.147	0.001*
C-Reactive Protein (mg/L)	0.980	0.949–1.012	0.224			
Albumin (g/dL)	0.928	0.724–1.190	0.557			

(*Continued*)

Table 2 (Continued).

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Combine with biologic therapy						
5-ASA	1.273	0.513–3.162	0.603			
Steroid	0.696	0.280–1.731	0.435			
Immunosuppressants	1.889	0.640–5.575	0.249			

Notes: *P < 0.05.Continuous data were presented as mean ± standard deviation. Categorical data were displayed as absolute numbers (percentage). Both were evaluated by univariate and multivariate logistic regression and the result were displayed.
Abbreviations: 5-ASA, 5-Aminosalicylic Acid; OR, Odds Ratio; CI, confidence interval.

95% CI: 1.296–34.852; P=0.023), ustekinumab use (OR: 5.672; 95% CI: 1.138–28.267; P=0.034), and hemoglobin levels (OR: 1.612; 95% CI: 1.210–2.147; P=0.001). The optimal cutoff value for hemoglobin was 11.65 g/dL (area under the ROC curve: 0.714, 95% CI: 0.610–0.818).

Discussion

In our study, approximately 20.94% of the IBD population had elderly-onset disease. Consistent with previous research,[6,7,9,12,26–28] elderly-onset UC tended to be milder. Ileal involvement in CD (44.23%) and extensive colitis in UC (58.18%) were common findings in our elderly population. However, the extent of disease in our study differs somewhat from previous literature. In recent studies, colonic involvement in CD and left-sided colitis in UC were more common in Western populations,[4,6,7,26,27,29,30] whereas ileal involvement in CD and proctitis in UC were predominant in Eastern populations.[7,12,29,31] Additionally, inflammatory phenotypes in elderly-onset CD were more frequent in the West, while stricturing phenotypes were more typical in the East,[7,12,29,30] Our study found a predominance of the inflammatory phenotype, suggesting a potential regional difference in disease presentation between Eastern and Western populations.

Vedolizumab, a monoclonal antibody targeting α4β7 integrin, has been shown to provide gut-selective anti-inflammatory activity.[32,33] Importantly, adverse events related to vedolizumab showed no significant difference between younger and elderly patients with CD and UC,[34,35] supporting its increased use in elderly-onset patients in our study.

Regarding drug persistence, our findings indicated no significant difference in 1-year drug persistence between elderly-onset and control groups in both CD and UC. This suggests that advanced therapies remain effective in elderly populations. However, ustekinumab demonstrated higher 1-year drug persistence compared to other biologic agents in the elderly-onset CD group, though no significant differences were observed in the UC cohort. Similar findings regarding ustekinumab's favorable persistence have been reported in other studies,[36,37] possibly reflecting the different efficacy profiles of therapies for managing CD and UC in elderly patients.

Older age has been identified as a predictive factor for drug persistence.[17,21] In our logistic regression analysis, three independent factors significantly influenced drug persistence in the elderly-onset group: Montreal L1, indicating isolated ileal involvement in CD, may represent a less severe disease course, which could contribute to better treatment adherence. Ustekinumab's safety and efficacy profile likely underpin its higher persistence in this population.[31,36–41] Additionally, higher hemoglobin levels were associated with better drug persistence, suggesting that patients with less severe anemia may have fewer disease complications and better overall health, allowing them to maintain treatment.[42–45]

Managing inflammatory bowel disease (IBD) in elderly patients requires personalized strategies due to comorbidities and increased treatment risks. Recent advancements in drug delivery systems, such as ROS-responsive nanoparticles, have enhanced therapeutic efficacy while minimizing side effects, offering promising options for improving outcomes in this population.[46,47] Advanced therapies, including Infliximab and Ustekinumab, demonstrate comparable outcomes and therapy persistence to younger patients. These findings underscore the importance of identifying key predictors and tailoring treatment approaches to optimize care for elderly-onset IBD patients, ensuring more effective and safer management of their condition.

This study has several limitations. First, it was conducted at a single academic center (Linkou Chang Gung Memorial Hospital), which may introduce referral bias. Second, as a retrospective cohort study, it is subject to biases such as selection

and information bias due to the reliance on existing medical records, which may contain incomplete or missing data. Third, there were only 52 elderly patients with Crohn's disease, which may introduce statistical bias. A larger sample size is required for further analysis and research. Finally, focusing on one-year drug persistence may not fully capture long-term outcomes, as IBD management typically requires long-term treatment. Future studies with longer follow-up periods are needed to better understand the sustainability of therapeutic responses and the potential for adverse events or complications over time.

Conclusion

Elderly-onset IBD presents distinct characteristics, with ileal involvement in CD and extensive colitis in UC, and shows favorable drug persistence with treatments like infliximab and ustekinumab. Montreal L1 classification, ustekinumab use, and hemoglobin levels are key predictors of drug persistence in elderly-onset patients, underscoring the need for tailored treatment approaches in this population. However, the regional generalizability of these findings should be acknowledged, as they are based on a single-center Taiwanese cohort.

Sample Data Availability Statements

The corresponding author would share the data underlying this article upon reasonable request.

Ethical Considerations

This study was approved by the Institutional Review Board (IRB) of the Chang Gung Medical Foundation (Approval No. 202400030B0: "Diagnosis, Treatment, and Prognosis of Inflammatory Bowel Disease"). Given the retrospective nature of the study, the IRB waived the requirement for signed informed consent for the use of medical records retrieved from the electronic medical record system.

To ensure participant privacy and data confidentiality, all patient information was anonymized before analysis. No identifiable personal data were disclosed or utilized in this study, and strict measures were implemented to maintain confidentiality in compliance with ethical and regulatory standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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