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Are the Clinical Course and Drug Toxicity Different in Late-Onset Inflammatory Bowel Disease Patients? From Tertiary Reference Center Real-Life Data

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Abstract

Objective: The rate of onset at a late age in Inflammatory Bowel Diseases (IBD) has increased over the years. The disease course and treatment outcomes remain uncertain in this group. We aimed to evaluate the disease course, drug toxicity, and prognosis of early and late-onset IBD patients.
Methods: The methodology involves a comprehensive retrospective review of medical charts of 1,060 patients diagnosed with IBD. Thirty-nine patients with late-onset IBD (≥60 years) were included in the study. As the control group, 50 early-onset patients with similar demographic characteristics to the late-onset patient group were included. Disease type, demographic data, treatments, treatment-related adverse effects and toxicities, mortality rates, extraintestinal and hepatobiliary involvement, and complications were compared between the early and late-onset groups.
Results: The mean age of the patients at the time of diagnosis was 49.2±17.5 years, and 53 (59.6%) were male. Among the 39 late-onset patients, 25 (64.1%) had UC; among the 50 early-onset patients, 28 (56.0%) had UC. AZT (azathioprine) toxicity (28% vs. 20.5%) and biological therapy toxicity (16% vs. 5.1%) were similar in both groups ($P>0.05$). Mortality was higher in late-onset patients (33.3% vs. 2%), as were complication rates in late-onset UC (32% vs. 7.1%) compared to early-onset patients ($P<0.05$). The malignancy rate was higher in late-onset patients, but this difference was not statistically significant (15.4% vs. 6%, $P>0.05$).
Conclusion: Late-onset IBD patients are similar to early-onset patients in terms of drug-related adverse effects. However, the mortality and complication rates are higher in late-onset patients, underscoring the importance of close follow-up in this patient group.
Keywords: Clinical course, drug toxicity, ınflammatory bowel disease, late-onset

INTRODUCTION

Inflammatory Bowel Diseases (IBD) are systemic chronic idiopathic inflammatory conditions that can affect the entire gastrointestinal system (GIS). Their etiology and pathophysiology remain unknown. These diseases are characterized by periods of remission and exacerbation and can lead to extra-intestinal manifestations. IBD primarily includes Crohn's disease (CD) and Ulcerative Colitis (UC). While most patients experience early onset, IBD can occur in all age groups, including pediatric and geriatric populations.[1,2] Current studies indicate that the prognosis for UC and Crohn's patients diagnosed at early and late ages varies. Although the treatment approach for late-onset IBD is fundamentally similar to that for early-onset adult patients, late-onset patients face higher mortality rates. This increase is due to polypharmacy, high comorbidities, decreased resistance to severe disease courses, complex drug interactions, and delayed diagnoses due to similar clinical presentations, which can lead to adverse side effects.[3] Therefore, careful consideration is necessary when selecting treatments.

The number of studies examining the disease course and response to treatment in late-onset IBD patients is insufficient. The limited clinical studies conducted in various regions indicate differences in disease progression and treatment response.[4,5] This study aims to compare late-onset IBD patients with early-onset ones concerning clinical and demographic data and to identify differences in the disease course.

MATERIALS AND METHODS

Study Design

Patients diagnosed with UC and CD, who had at least a six-month follow-up period in the Istanbul University Gastroenterology Outpatient Clinic, were included in this study. The medical records of 1,060 IBD patients, who had regular and active follow-up over the past decade in our outpatient clinic, were reviewed retrospectively. Patients aged 60 years or older were classified as having late-onset IBD, while those diagnosed at an earlier age were classified as having early-onset IBD. The study included 39 late-onset patients and 50 early-onset patients as

the control group. The control group consisted of patients with demographic characteristics similar to those of the late-onset patients. Patients with a follow-up period of less than six months, those who did not follow up regularly, and those diagnosed with indeterminate colitis were excluded from both the study and control groups.

In the study, various demographic and clinical data were collected for the patients. These included sex, age, disease type, age of onset, area of involvement, follow-up period, disease duration, initial and final disease type, family history, smoking history, conventional and biological treatments post-diagnosis, response to steroid treatment, endoscopic findings, development of treatment-related toxicity and side effects, presence of clinical and endoscopic remission, history of surgery, disease activity scores at first and last admission, presence of hepatobiliary and extraintestinal involvement, number of attacks post-diagnosis, complication development, laboratory values at diagnosis, and patient survival. The effects of these factors on the clinical course and patient prognosis were investigated.

The activity of the disease in UC patients was determined using the "Simple Clinical Colitis Activity Index" (SCCAI) score, and the endoscopic activity index was determined using the "Mayo" score.[6,7] Patients with an SCCAI score greater than 5 were considered to have active disease, while those with a score less than 5 were considered to be in remission. According to the Mayo score, patients scoring 0 or 1 were considered to be in remission, those scoring 2 were considered to have moderately active disease, and those scoring 3 were considered to have active disease. For CD patients, disease activity was assessed using the "Crohn's Disease Activity Index" (CDAI) score, and endoscopic activity was assessed using the "Simple Endoscopic Score for Crohn's Disease" (SES-CD).[8,9] Patients with a CDAI score less than 150 were considered to be in remission, those with a score between 150 and 450 were considered to have active disease, and those with a score greater than 450 were considered to have severely active disease. For the SES-CD score, patients scoring between 0 and 2 and those scoring between 3 and 6 were considered to be in remission, those scoring between 7 and 15 were considered to have moderately active disease, and those scoring greater than 15 were considered to have active disease. In operated CD patients, the endoscopic activity index was determined using the "Rutgeerts" score.[10]

Ethical Consideration

This retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration. The Ethical Committee of the Istanbul University Faculty of Medicine approved this study (Approval Number: 728364, Date: 31.01.2022). As this study was retrospective, it was carried out with general patient consent without the need for obtaining informed consent.

MAIN POINTS

- Late-onset patients exhibit similar immunomodulatory and biological therapy-related adverse effects compared to early-onset patients.
- The mortality and complication rates are higher in late-onset IBD patients.
- The disease course of patients with late-onset tends to be worse compared to those with early onset.
- Surveillance of late-onset patients is very important and clinical follow-up periods for these patients should be determined individually.

Statistical Analyses

The data obtained in the study were evaluated using SPSS v26.0 (IBM, Chicago, USA) for statistical analysis. Descriptive statistics were presented as mean, standard deviation, frequency, and ratio values. The normality distribution of variables was assessed with the Kolmogorov-Smirnov test. The Mann-Whitney U test was employed for the analysis of quantitative independent data. The chi-square test was used for analyzing qualitative independent data, and Fisher's exact test was applied when the conditions for the chi-square test were not met. A p-value of ≤0.05 was considered statistically significant in the comparison of paired groups.

RESULTS

Of the 1,060 patients screened, 39 (3.6%) had late-onset IBD. While 39 late-onset patients were included in the study, 50 early-onset patients were included as the control group, resulting in a total of 89 early and late-onset patients. The control group consisted of patients with demographic characteristics similar to those of the late-onset patients. The demographic characteristics of the patients are presented in Tables 1 and 2.

Comparative clinical characteristics of all patients are summarized in Table 3. Disease localization for both early and late-onset patients was determined according to the Montreal classification.[11]

There was no statistically significant difference between early-onset and late-onset patients in terms of hepatobiliary involvement (44% vs. 46.2%; OR: 1.09, CI: 0.47-2.5; *P*=0.50). Extraintestinal involvement was also similar between the two groups (62% vs. 61.5%; OR: 0.98, CI: 0.4-2.3; *P*=0.56).

Table 1. Demographic Characteristics of CD Patients

	Early onset (<60 years), n=22	Late-onset (≥60 years), n=14	P
Age, years (mean±SD)	42.9±10	75±7.9	**< 0.05**
Sex, F/M (n, %)	7 (31.8) / 15 (68.2)	6 (42.9) / 8 (57.1)	> 0.05
Smoking status, n			> 0.05
Current	4	2	
Former	6	8	
Never smoked	12	4	
Age at diagnosis, years (mean±SD)	33.4±10.5	67.5±5.9	**< 0.05**
Disease duration, months (mean±SD)	113.4±36.1	99.4±91.3	> 0.05
Follow-up time, months (mean±SD)	99.3±32	67.9±62.9	> 0.05
Family history of IBD, n	3	0	> 0.05

Table 2. Demographic Characteristics of UC Patients

	Early onset (<60 years), n=28	Late-onset (≥60 years), n=25	P
Age, years (mean±SD)	49.5±12.3	75.2±7.1	**< 0.05**
Sex, F/M (n, %)	13 (46.4) / 15 (53.6)	10 (40) / 15 (60)	> 0.05
Smoking status, n			> 0.05
Current	4	2	
Former	10	14	
Never smoked	14	9	
Age at diagnosis, years (mean±SD)	37.7±10.8	65.7±5.2	**< 0.05**
Disease duration, months (mean±SD)	137.7±55.5	106.6±47.3	**< 0.05**
Follow-up time, months (mean±SD)	107.5±43.1	79.1±47.7	**< 0.05**
Family history of IBD, n	1	3	> 0.05

Table 3. Comparative Representation of Clinical Characteristics of Patients

	Crohn's disease			Ulcerative colitis		
n (%) Age of onset	**<60 years**	**≥60 years**	**P**	**<60 years**	**≥60 years**	**P**
AZT toxicity	6 (27.3)	3 (21.4)	0.50	8 (28.6)	5 (20)	0.34
AZT onset	22 (100)	11 (78.6)	0.051	19 (67.9)	11 (44)	0.07
AZT discontinuation	13 (59.1)	5 (35.7)	0.15	5 (17.9)	8 (32)	0.19
Non-biological tx adverse events	5 (22.7)	0 (0)	0.07	4 (14.3)	4 (16)	0.58
Complication	11 (50)	3 (21.4)	0.08	2 (7.1)	8 (32)	**0.02**
Mortality	0 (0)	3 (21.4)	**0.05**	1 (3.6)	10 (40)	**0.001**
Hepatobiliary involvement	12 (54.5)	6 (42.9)	0.36	10 (35.7)	12 (48)	0.26
Extraintestinal involvement	17 (77.3)	9 (64.3)	0.31	14 (50)	15 (60)	0.32
Biological use	15 (68.2)	5 (35.7)	0.058	10 (35.7)	4 (16)	0.09
Biological tx adverse events	5 (22.7)	1 (7.1)	0.22	3 (10.7)	1 (4)	0.35
Operation	9 (40.9)	4 (28.6)	0.34	3 (10.7)	6 (24)	0.17
Intestinal malignancy	0 (0)	1 (7.1)	0.38	0 (0)	1 (4)	0.47
Extraintestinal malignancy	0 (0)	1 (7.1)	0.38	3 (10.7)	5 (20)	0.28

AZT= Azathioprine, Tx=treatment

The mortality rate was higher among late-onset IBD patients compared to those in the early-onset group (33.3% vs. 2%; OR: 24.5, CI: 3-197.8; *P*=0.001). When considering disease subgroups, mortality rates in late-onset versus early-onset patients were 21.4% vs. 0% in CD patients (*P*=0.05), and 40% vs. 3.6% in UC patients (OR: 18, CI: 2.1-154.5; *P*=0.001). The causes of mortality in patients with early and late-onset IBD are shown in Table 4.

There were no significant differences in complication rates between early-onset and late-onset patients (26% vs. 28.2%; OR: 1.1, CI: 0.4-2.8; *P*=0.50) (Table 5). However, complication rates were higher in late-onset UC patients compared to early-onset UC patients (32% vs. 7.1%; OR: 6.1, CI: 1.1-32.3; *P*=0.02) and in CD patients compared to UC patients (38.9% vs. 18.9%; *P*=0.03). While no cases of intestinal malignancy developed in early-onset IBD patients, it was detected in two late-onset patients, although this was not statistically significant (0% vs. 5.1%; *P*=0.18).

The discontinuation rate of AZT was higher in CD patients than in UC patients (54.5% vs. 43.3%; OR: 0.3, CI: 0.1-0.8; *P*=0.01). Discontinuation rates of AZT treatment were similar between early-onset and late-onset patients (36% vs. 33.3%; OR: 0.89, CI: 0.37-2.1; *P*=0.48). Additionally, AZT toxicity rates were comparable between the two groups (28% vs. 20.5%; OR: 0.6, CI: 0.2-1.8; *P*=0.28). The AZT toxicities in patients are presented in Table 6.

Table 4. Causes of Mortality in Early and Late-onset Patients

Cause of mortality	Early-onset (<60 years), n	Late-onset (≥60 years), n	P
Extraintestinal malignancy	1	4	
IBD exacerbation	--	2	
Septic shock	--	1	
Myocardial infarction	--	1	*0.001*
Dementia worsening	--	1	
Orthopedic trauma	--	1	
No information	--	2	

Table 5. Complications Seen in Early and Late-onset Patients

	Early-onset (<60 years), n	Late-onset (≥60 years), n	P
Abscess	8	2	
Ileus	6	2	
Malignancy	--	2	
Perforation	--	2	
Toxic megacolon	--	1	0.50
Osteoporosis	2	5	
Massive bleeding	1	--	
Renal infarction (thrombosis)	--	1	
Epilepsy	--	1	

Table 6. AZT-related Toxicity in Patients

	Early onset (<60 years), n	Late-onset (≥60 years), n	P
Major			
Neutropenia	6	6	
Pancreatitis	2	0	
Hepatotoxicity	3	1	
Minor			0.28
GIS intolerance	5	4	
Rash	6	2	
Flu-like illness	--	--	
Total	22	13	

The rate of biological therapy usage was higher among early-onset patients compared to late-onset patients (50% vs. 23.1%; OR: 0.3, CI: 0.12-0.76; *P*=0.008). When comparing UC and CD patients in terms of receiving biological therapy, the rate was higher in CD patients (55.6% vs. 26.4%; OR: 0.28, CI: 0.1-0.7; *P*=0.005).

The rates of biological therapy-related side effects were similar in both patient groups (32% vs. 22.2%; OR: 0.28, CI: 0.05-1.4; *P*=0.09). The specific side effects included secondary infection in one patient using adalimumab, rash in four patients using infliximab, dyspnea in two patients, itching in two patients, secondary infection in one patient, palpitation in one patient, and neuropathy in one patient.

There was no relationship between smoking and mortality, operation, or intestinal malignancy in our patient group. However, a statistically significant negative correlation was found between smoking and response to steroid treatment (*r*=-0.257; *P*=0.03).

Early-onset IBD patients who developed AZT toxicity were found to have a high risk of side effects with biologic therapy (OR: 35, CI: 0.3-337; *P*=0.001).

DISCUSSION

There has been a noticeable rise in the number of late-onset IBD patients over the past few decades. Additionally, the proportion of aging patients transitioning from early-onset IBD is increasing. In our patient group, the rate of late-onset IBD diagnoses in the last few decades stands at 3.6%. Diagnosing IBD, particularly in the advanced age group, can be challenging due to the prevalence of diseases in the differential diagnosis, such as NSAID-related enterocolitis, infectious enterocolitis, microscopic colitis, diverticulitis, and ischemic colitis. These conditions share similar symptoms with IBD, potentially leading to delays in diagnosis. A delayed diagnosis has detrimental effects on patients' quality of life, promotes disease progression, reduces the efficacy of treatment, increases the likelihood of disease-related complications, and raises the need for surgery.[12,13]

While the treatment for late-onset IBD patients shares similarities with that of early-onset patients, managing and selecting treatments for the older age group requires careful consideration. Factors such as polypharmacy, increased frailty, reduced resistance to severe diseases, complex drug interactions, and comorbidities necessitate a nuanced approach. Notably, there is a lack of standardized approaches for the follow-up and treatment of late-onset patients. The existing literature falls short in terms of studies comparing early and late-onset patients, analyzing the disease's course, and assessing treatment responses in the latter. The limited clinical studies conducted across different regions reveal variations in disease progression, prognosis, and response to treatment among late-onset patients.

An Italian study comparing late-onset and early-onset UC patients found more complications but less extraintestinal involvement in late-onset patients.[14] Consistent with this, we observed a higher complication rate in late-onset UC patients compared to early-onset patients (*P*=0.02), and complications were more prevalent in CD compared to UC (*P*=0.03). However, no statistically significant difference emerged between early-onset and late-onset patients in terms of extraintestinal involvement.

A Spanish study examining late-onset IBD patients reported that AZT efficacy and toxicity rates were similar to those in early-onset patients.[15] Similarly, in our study, no statistically significant difference was found between the groups regarding AZT toxicity.

In two studies conducted in the US and UK, involving both early and late-onset UC patients, the observed mortality rates were consistent with those of the general population.[16,17] Similarly, a study from Greece reported a comparable disease course for both groups.[18] A systematic review with meta-analysis indicated that the mortality rate among late-onset IBD patients aligns with that of the general population.[19] However, various studies present conflicting findings, with some reporting higher and others reporting lower mortality rates for late-onset patients compared to their early-onset counterparts.[20,21] In Norwegian and US studies exploring both early and late-onset IBD patients, elevated mortality rates were reported in the late-onset group.[20,22] Similarly, we found that late-onset patients had a significantly higher mortality rate (*P*=0.001).

Cardiovascular diseases are frequently cited as the main cause of mortality in patients with IBD, followed by intestinal and extraintestinal malignancies.[23] The heightened incidence of malignancies in these patients is linked to systemic inflammation resulting from IBD and the use of immunomodulatory or anti-TNF drugs in treatment. In this study, the usage of AZT and biological agents was lower in the elderly group, making it challenging to attribute the development of malignancy in this group to drug use. Chronic inflammation also increases the frequency of cardiovascular events and dementia in IBD patients.[24,25] The higher mortality rate observed in late-onset patients may be attributed to the immunological, cardiovascular, and neurological effects of chronic inflammation caused by IBD and its treatment, along with the high prevalence of comorbidities in this late-onset group.

The frequency of systemic inflammation and immunomodulatory and anti-TNF therapy-associated lymphoproliferative, skin, and solid organ malignancies is increased in IBD patients.[26,27] Since cervical and other gynecological malignancies are seen more frequently in IBD patients, it is recommended that female IBD patients undergo regular obstetric screening.[26,28] In this study, there were no patients with hematological lymphoproliferative malignancies. However, there were cases of other malignancies: 2 patients had breast cancer, 1 patient had a spindle cell tumor, 1 patient had bladder cancer, 1 patient had a parotid gland tumor, and 1 patient had pancreatic mucinous cystadenocarcinoma.

In a Chinese study examining the development of malignancy in late and early-onset IBD patients between 1998 and 2020, it was reported that both intestinal and extraintestinal malignancies were more common in the late-onset group.[29] In our study, no intestinal malignancies developed in early-onset IBD patients, whereas they were detected in 2

late-onset patients; however, this difference was not statistically significant (P=0.18). When comparing early and late-onset patients in terms of extraintestinal malignancies, 3 early-onset patients and 6 late-onset patients developed such malignancies. While these findings are consistent with those reported in the literature, they did not reach statistical significance (P>0.05). This lack of significance may be due to the small sample size in this study.

A Belgian study compared the side effects of anti-TNF therapy between early-onset and late-onset IBD patients and reported that the rate of serious side effects was higher in late-onset patients.[30] Interestingly, no serious allergic reactions or side effects related to biologic therapy were observed in our study, which may be attributed to the relatively small sample size. Except for severe side effects, there was no statistically significant difference in terms of biological therapy side effects (P=0.09). However, it was determined that the risk of developing biological drug side effects increased in early-onset patients who also experienced AZT side effects (OR: 35, CI: 0.3-337; P=0.001).

The most important limitation of this study is the small number of late-onset patients over the past decades. Although clinical and endoscopic remission rates were lower in the late-onset group, statistical significance was not observed. This lack of significance may become notable as the number of cases increases. Additionally, due to the retrospective nature of our study, the lack of endoscopic controls at standard intervals may have also affected the remission rates.

In conclusion, the mortality rate was found to be higher in late-onset patients. The side effects associated with AZT and biological therapy were similar in both early and late-onset patients. However, the late-onset group exhibited a higher complication rate, highlighting the importance of close monitoring and follow-up for these patients. Despite the increased complications, the treatment approach required by the disease can be applied similarly to the early age group, provided there is close follow-up.

Ethics Committee Approval: The Ethical Committee of the Istanbul University Faculty of Medicine approved this study (Approval Number: 728364, Date: 31.01.2022).

Informed Consent: As this study was retrospective, it was carried out with general patient consent without the need for obtaining informed consent.

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