

Increasing challenges of inflammatory bowel disease in a Turkish cohort (2006-2016)

I. Yuksel^{1,2}, S. Kilincalp¹, Y. Coşkun¹, H. Akinci¹, F. Karaahmet¹, M. Hamamci¹

(1) Department of Gastroenterology, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey ; (2) Department of Gastroenterology, Ankara Yildirim Beyazit University School of Medicine, Ankara, Turkey.

Abstract

Background : We aimed to describe the natural course of inflammatory bowel disease (IBD) in adult Turkish patients during the past decade.

Methods : We performed a retrospective investigation in total 508 patients with IBD between 2006 and 2016. The severity of IBD was assessed by the need for hospitalization, biological therapy and surgery. The study consisted of 304 (59.8%) patients with UC, 180 (35.4%) with CD and 24 (4.7%) IBD unclassified patients.

The ratio of severe disease for both CD and UC was as follows: hospitalization in 71 (39.4%) and 37 (12.2%), biological therapy received in 20 (11.1%) and 3 (1.0%), and surgery in 23 (12.8%) and 2 (0.7%) respectively.

Patients were divided into two groups based on the date of disease onset. Earlier group includes the patients followed-up between 2006-2011 and later group, between 2011-2016. Our results revealed that the proportion of patients receiving biological therapies was significantly higher and the rate of surgery was significantly lower in the later group compared to the earlier group (14.5% to 0%, 9.4 to 23.8, respectively). The hospitalization rate was lower in the later group compared to earlier group but did not reach a significant difference (37.7% to 45.2% respectively).

Conclusions : The course of IBD in Turkish patients appears to be between that of Europe and Asia. In patients with CD, proportion of patients receiving biologic therapy has increased while rate of surgery has decreased. (*Acta Gastroenterol. belg.*, 2018, 81, 373-380).

Keywords: Inflammatory bowel disease, Crohn's disease, Natural Course

Introduction

Multiple studies have reported the epidemiology, gender distribution and natural course of inflammatory bowel diseases (IBD) in North America and Western Europe (1,2). Incidence of Ulcerative Colitis (UC) has stabilized, while that of Crohn's disease (CD) has continually increased in western countries in the past five decades (2,3). However, in the developing countries and Asia, studies have demonstrated that the incidences of both UC and CD have increased (4,5). In CD, with increasing numbers of patients and longer follow up, more changes in phenotype can be seen (2,6). During the first few years of CD, inflammatory forms predominate, whereas after 40 years of disease, most patients have experienced additional phenotypes, with penetrating being more common than structuring (2,7). Based on several Western studies, 70%-80% of patients with CD require intestinal surgery within 20 years of disease

duration (8,9,10). For CD, studies in Asia have shown a more favorable clinical course than that in western studies. However, recent studies suggest that the natural history of IBD in Asia is becoming similar to that of the West (11,12).

The incidence and disease progression of IBD in Turkey has not been investigated extensively in previous studies. We performed a hospital-based study to investigate frequency, gender, and characteristic features of IBD in Turkey.

Material and Methods

Data Collection and Definitions

The medical records of adult IBD patients admitted into our tertiary gastroenterology clinic between November 2006 and September 2015 were reviewed. Only patients with at least 6 months of follow-up data were included in the study. The diagnosis of IBD was made and patients were classified as CD, UC and IBD unclassified. The Montreal classification was used to define location, behavior of CD and the extent of UC (14). The term IBDU was defined according to the Copenhagen diagnostic criteria and used for the patients who did not meet the diagnostic criteria for either CD or UC after extensive diagnostic work-up but who needed relevant IBD treatment (15). In the study group, upper gastrointestinal involvement (Upper intestinal small bowel wall thickening and hyperenhancement) was assessed by MR enterography and/or CT enterography.

Those patients having a history of major abdominal surgery due to IBD were included under the heading Surgery. Severity of IBD was assessed through the need for hospitalization related to IBD, whether biological therapy was received and/or whether surgery was

Correspondence to : İlhami YUKSEL, MD, Yildirim Beyazit University, School of Medicine, Department of Gastroenterology, Üniversiteler Mahallesi İhsan Doğramacı Bulvarı No:6 (06100) Bilkent Çankaya/Ankara, Turkey. Gayret Mah İstiklal Caddesi Oruç Reis Sokak CK-4 no:19 Yenimahalle / Ankara, Turkey
E-mail: yukselilhami@hotmail.com

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Table 1. — Demographic characteristics, disease location and behaviour of patients with inflammatory bowel disease

	UC n: 304 (59.8%)	CD n: 180 (35.4%)	IBDU n: 24 (4.7%)	Total IBD n: 508
Age at onset of IBD (years ± SD)	40.2 ± 13.4	38.8 ± 13.1	40.6 ± 15.7	39.7 ± 13.4
Duration of disease (months ± SD)	48.0 ± 28.4 ^a	22.5 ± 25.2	23.3 ± 23.7	37.7 ± 29.8
Males, n (%)	186 (61.2%)	116 (64.4%)	15 (62.5%)	317 (62.4%)
Current smokers	27 (8.9%)	69 (38.3%) ^b	0	96 (18.9%)
Appendectomy	6 (2%)	18 (10%) ^c	0	24 (4.7%)
Family History	20 (6.6%)	11 (6.1%)	0	31 (6.1%)
Disease extent				
Proctitis	82 (26.9%)			
Left-sided colitis	133 (43.8%)			
Extensive colitis	89 (29.3%)			
Ileal (L1)		79 (43.9%)		
Colonic (L2)		8 (4.4%)		
Ileo-colonic (L3)		93 (51.7%)		
Combined with upper GI disease		30 (16.7%)		
CD phenotypes				
Non-stenosing non-penetrating (B1)		147 (81.6%)		
Stenosing (B2)		12 (6.7%)		
Penetrating (B3)		21 (11.7%)		
P (Perianal disease)		31 (17.2%)		
Maintenance of Remission				
Mesalazine oral	148 (48.7%)	48 (26.7%)	13 (54.2%)	209
Mesalazine enema	162 (53.3%)	8 (4.4%)	8 (33.3%)	178
Mesalazine supp	65 (21.4%)	0	2 (8.3%)	67
Sulfasalazine	4 (1.3%)	8 (4.4%)	1 (4.2%)	13
Azathioprine	24 (7.9%)	64 (35.6%)	3 (12.5%)	91
Methotrexate	1 (0.3%)	10 (5.6%)	0	11
Adalimumab	2 (0.7%)	11 (6.1%)	1 (4.2%)	14
Infliximab	1 (0.3%)	9 (5%)	0	10
Steroid Dependence	16 (5.3%)	17 (9.4%)	3 (12.5%)	36 (7.1%)
Hospitalization	37 (12.2%)	71 (39.4%) ^d	5 (20.8%)	113 (22.2%)
Biological treatment	3 (1.0%)	20 (11.1%) ^e	1 (4.2%)	24 (4.7%)
Surgery	2 (0.7%)	23 (12.8%) ^f	0	25 (4.9%)

Duration of disease in patients with UC is significantly higher than in those with CD (a, $p < 0.001$)

The rates of active smokers, appendectomy, steroid dependence, hospitalization, biological treatment and surgery is significantly higher in those with CD compared to UC (b, c, d, e, f: $p < 0.001$).

undergone due to IBD. To investigate whether the frequency and nature of CD and UC have changed during between 2006 and 2015, the cohort was divided into two subgroups according to the date of diagnosis. Patients with less than a 6-month follow-up period were excluded from the study. In order to make accurate comparisons with regard to follow-up times to compare the data between the earlier and later groups, patients in both groups were evaluated in an equal time interval. In the earlier group, patients were diagnosed with IBD between November 2006- January 2011 (followed-up

between November 2006-June 2011). The later group includes patients diagnosed with IBD at least 6 months after the upper limit of the date range of the earlier group. The later group includes patients diagnosed with IBD between June 2011-September 2015 (followed-up between June 2011-January 2016).

Statistical Analysis

SPSS software (SPSS 16.0, Chicago, USA) was applied. Data was expressed as means ± standard

deviation. Kruskal-Wallis test was used to compare the parameters of groups. Chi-square test was used to compare the categorical variables. Logistic regression was utilized for a multivariate analysis of risk factors for hospitalization surgery and biological treatment. The factors significant in univariate analyses at $P \leq 0.05$ were included in the final multivariate models to estimate the odds ratios (OR) and 95% confidence intervals. A p-value cut-off ≤ 0.05 was considered as statistically significant. Subgroup analysis was performed among individuals with CD and UC.

Ethical statement

This study was approved by the ethics committee of our institute.

Results

Patient Characteristics

A total of 508 adult patients diagnosed with IBD between November 2006 and September 2015 were enrolled in this study. The study consisted of 306 (59.8%) UC patients, 180 (35.4%) CD patients and 24 (4.7%) IBDU patients. The demographic characteristics of patients are shown in Table 1. The mean age at diagnosis for all IBD patients was 39.73 years (range 16-84 years). The mean age at diagnosis in UC, CD and IBDU were 40.2, 38.8, and 40.6 years, respectively.

The proportion of male patients was higher than female patients in the total IBD group (317, 62.4% to 191, 37.6%) and in UC (186, 61.2% to 118, 38.8%), CD (116, 64.4% to 64, 35.6%) and IBDU (15, 62.5% to 9, 37.5%) subgroups. As for gender distribution, the female: male ratio was 1:1.57 for UC and 1:1.81 for CD.

We analyzed the association of cigarette smoking with both diseases. The proportion of active smokers was significantly higher in the CD group compared to the UC group (38.3%, 8.9%, respectively) ($p < 0.001$). The frequency of appendectomy in the CD patients (10%) was significantly higher than in UC patients (2%) ($p < 0.001$). There was no statistically significant difference among the UC and CD groups in positive family history of IBD (6.6%-6.1%, respectively) (Table 1).

Disease Extent, Localization, and Behavior

Of the total 304 (59.8%) patients diagnosed with UC, 82 displayed proctitis (26.9%), 133 showed left sided colitis (43.8%) and 89 extensive colitis (29.3%). Crohn's disease was diagnosed in 180 patients (35.4%), combined with ileal (79, 43.9%), colonic (8, 4.4%), ileo-colonic (93, 51.7%) and upper GI involvement (30, 16.7%). Among the CD patients; non-stenosing non-penetrating disease was found in 147 (81.6%), stenosing in 12 (6.7%), penetrating in 21 (11.7%), perianal disease in 31 (17.2%). 24 (4.7%) patients were diagnosed with IBDU. These findings are summarized in Table 1.

Medical Treatment

Azathioprine was mostly used for maintenance of remission in CD ($n = 64$, 35.6%), while mesalazine enema ($n = 162$, 53.3%) and mesalazine oral ($n = 148$, 48.7%) were used in UC for this purpose. In CD patients, mesalazine oral ($n = 48$, 26.7%), mesalazine enema ($n = 8$, 4.4%), sulfasalazine ($n = 8$, 4.4%), and methotrexate ($n = 10$, 5.6%) were also used for the maintenance of remission. In the UC group, compared to CD, a smaller group of patients received other medical treatment options including azathioprine ($n = 24$, 7.9%), sulfasalazine ($n = 4$, 1.3%), and methotrexate ($n = 1$, 0.3%) for the maintenance of remission. Biological treatment was administered to 20 (11.1%) CD patients: 11 (6.1%) were treated with adalimumab and 9 (5.0%) received infliximab. In patients with UC, adalimumab ($n = 2$, 0.7%) and infliximab ($n = 1$, 0.3%) were used for the maintenance of remission. Steroids dependence was similar in patients with CD ($n = 17$, 9.4%) and in patients with UC ($n = 16$, 5.3%). Demographic characteristics and medical treatments for the maintenance of remission of patients with inflammatory bowel disease are shown in Table 1.

Disease Severity and Associated Factors

The severity of IBD was assessed by the need for hospitalization, biological therapy and abdominal surgery related to IBD. Disease severity indicators in patients with CD and UC were as follows: hospitalization in 71 (39.4%) and 37 (12.2%), biological therapy in 20 (11.1%) and 3 (1.0%), and surgery in 23 (12.8%) and 2 (0.7%) respectively. Thus the CD group showed a significantly higher proportion of these three severity indicators compared to UC ($p < 0.001$) (Table 1). When we performed a subgroup analysis which studied the relationship between severity indices and demographic factors among CD patients, we observed that hospitalized patients displayed a statistically significant longer duration of disease (28.1 months versus 18.9 months, $p = 0.019$), appendectomy (16.5% versus 5.5%, $p = 0.006$), steroid dependence (22.5% versus 0.9%, $p < 0.001$), and presence of peripheral arthropathy (21.1% versus 6.4%, $p = 0.008$), when compared to the non-hospitalized CD group (Table 2 and 3).

Moreover we also observed that among the CD patients, those receiving biological treatment showed a statistically significant longer duration of disease (29.1 versus 21.6 months, $p = 0.014$), and higher rates for the female gender (60% versus 32.5%, $p = 0.03$), appendectomy (30% versus 7.5%, $p = 0.007$), steroid dependence (70% versus 1.9%, $p < 0.001$), and axial joints involvement (20% versus 9.4%, $p = 0.047$) compared to those not receiving biological treatment in the CD group (Table 2 and 3). We also studied the association of surgery and demographic factors. We observed that there was a significant difference between the surgery and

Table 2. — Disease severity, location, behaviour and associated demographic factors in patients with CD

Crohn's Disease n: 180	Hospitalizations		Biological treatment		Surgery	
	Yes n: 71 (39.4%)	No n: 109 (60.6%)	Yes n: 20 (11.1%)	No n: 160 (88.9%)	Yes n: 23 (12.8%)	No n: 157 (87.2%)
Age at onset of CD	36.9±13.9	40.0±12.5	36.1±11.4	39.1±13.3	43.6±14.8	38.1±12.7
Duration of disease	28.1±25.9 ^a	18.9±24.3	29.1±18.9 ^b	21.6±25.9	28.1±28.2	21.6±24.8
Female, n (%)	29 (40.8%)	35 (32.1%)	12 (60%) ^c	52 (32.5%)	13 (56.5%) ^d	51 (32.5%)
Current smokers	25 (35.2%)	44 (40.4%)	4 (20%)	65 (40.6%)	7 (30.4%)	62 (39.5%)
Appendectomy	12 (16.9%) ^e	6 (5.5%)	6 (30%) ^f	12 (7.5%)	3 (13%)	15 (9.6%)
Family History	5 (7%)	6 (5.5%)	3 (15%)	8 (5%)	0	11 (7%)
Steroid Dependence	16 (22.5%) ^g	1 (0.9%)	14 (70%) ^h	3 (1.9%)	4 (17.4%)	13 (8.3%)
Ileal (L1)	24 (33.8%)	55 (50.5%)	10 (50%)	69 (43.1%)	11 (47.8%)	68 (43.3%)
Colonic (L2)	4 (5.6%)	4 (3.7%)	2 (10%)	6 (3.8%)	1 (4.3%)	7 (4.5%)
Ileo-colonic (L3)	43 (60.6%)	50 (45.9%)	8 (40%)	85 (53.1%)	11 (47.8%)	82 (52.2%)
Combined with upper GI disease	14 (19.7%)	16 (14.7%)	5 (25%)	25 (15.6%)	1 (4.3%)	29 (18.5%)
Non-stenosing non-penetrating (B1)	39 (54.9%)	106 (97.2%)	8 (40%)	139 (86.9%)	0 (%)	147 (93.6%)
Stenosing (B2)	11 (15.5%) ⁱ	1 (0.09%)	7 (35%) ^j	5 (3.1%)	5 (21.7%) ^k	7 (4.5%)
Penetrating (B3)	21 (29.6%) ^l	0 (%)	5 (25%) ^m	16 (10%)	18 (78.3%) ⁿ	3 (1.9%)
P (Perianal disease)	17 (23.9%)	14 (12.8%)	4 (20%)	27 (16.9%)	2 (8.7%)	29 (18.5%)
Extraintestinal Manifestation						
Peripheral arthropathy	15 (21.1%) ^o	7 (6.4%)	1 (5%)	21 (13.5%)	3 (13%)	19 (12.1%)
Eye	0	1 (0.9%)	0	1 (0.6%)	0	1 (0.6%)
Skin	5 (7%)	1 (0.9%)	1 (5%)	5 (3.1%)	1 (4.3%)	5 (3.2%)
Axial arthropathy	7 (9.9%)	12 (11%)	4 (20%) ^p	15 (9.4%)	0	19 (12.1%)
PSC	1 (1.4%)	0	1 (5%)	0	0	1 (0.6%)
Oral Aphthous Ulcer	2 (2.8%)	8 (7.3%)	0	10 (6.3%)	0	10 (6.4%)

Duration of disease, appendectomy, steroid dependence and peripheral arthropathy in hospitalized patients with CD showed a significant increase cf. non hospitalized patients ($p=0.019^a$, $p=0.006^e$, $p<0.001^g$, $p=0.008^o$)

Duration of disease, female gender, appendectomy, steroid dependence and axial arthropathy in biological therapy group were significantly higher than in the non biological therapy group ($p=0.014^b$, $p=0.03^c$, $p=0.007^f$, $p<0.001^h$, $p=0.047^p$)

The number of female CD patients in the surgery group was significantly higher than those in the non surgery group ($p=0.044^d$)

Stenosing and penetrating phenotypes were significantly increased in hospitalized, biological therapy and surgery groups, (0.001^i , $p=0.005^j$ and $p<0.001^l$, $p=0.045^m$, $p<0.001^o$, respectively).

non-surgery groups in gender and CD phenotypes. More women than men underwent surgery (56.5% versus 32.5%, $p=0.044$). Also the occurrence of the stenosing and penetrating phenotype in hospitalized, biological treatment and surgery groups was significantly higher than for those not receiving such treatment (Table 2 and 3).

Disease frequency and severity in the Earlier and Later Groups

In order to ascertain disease evolution of UC and CD thoroughly, we divided the UC and CD groups into two subgroups according to date at diagnosis. For both UC and CD, increases in disease frequency and severity were

greater in the later groups, ranging from 100 (32.9%) in the earlier UC group to 204 (67.1%) in the later UC group, and from 42 (23.3%) in the earlier CD group to 138 (76.7%) in the later CD group (Table 4). Increasing trends were slightly more prominent in CD compared to UC moving from earlier to later groups, the ratio was 71.4% and 59.6% for UC and 29.6% to 40.4% for CD from earlier to later groups, respectively.

Mean age at onset of UC and CD was similar in the earlier and later groups. Disease duration in the earlier group was greater than in the later group for both UC (42.4 ± 20.0 months versus 13.9 ± 14.9 months, $p<0.001$) and CD (57.9 ± 6.4 versus 32.3 ± 15.7 months, $p<0.001$). There was no statistical difference among the

Table 3. — Odds ratios (95% CI) for hospitalization, biological treatment and surgery of specific risk factors in patients with Crohn's disease

Variables	Hospitalization			Biological treatment			Surgery		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Duration of disease	1.01	1.00-1.02	0.02	1.010	0.99-1.02	<0,001			N/S
Gender									
Female (ref)	1.0		0.05	1.0		0.02	1.0		0.029
Male	1.4	0.78-2.71		3.11	1.20-8.08		2.70	1.11-6.57	
Appendectomy									
No (ref)	1.0		0.01	1.0		0.04			N/S
Yes	3.49	1.2-9.7		5.28	1.7-16.2				
Steroid Dependence									
No (ref)	1.0		0.004	1.0		<0.001			N/S
Yes	4.91	1.69-14.62		122.1	27.5-541.7				
CD phenotypes									
Non-stenosing/ non-penetrating (B1) (ref)	1.0								
Stenosing (B2)	3.46	3.8-243.7	<0,001	16.09	4.6-60.0	<0,001	5.95	1.7-20.7	0.005
Penetrating (B3)	4.16	1.1-18.2	<0,001	3.02	0.9-9.3	0.042	184.8	40.7-838.4	<0,001
Extraintestinal Manifestation									
Periphral arthropathy									
No (ref)	1		0.005			N/S			N/S
Yes	3.9	1.5-10.1							
Axial arthropathy			N/S						
No (ref)	1.0			1.0		0.017			N/S
Yes				2.41	0.7-8.1				

Table 4. — According to Earlier Group (2006-2010) and Later Group (2011-2016), features and disease severity of patients with CD and UC

	CD n: 180		P- value	UC n: 304		P-value
	Earlier Group (2006-2011) n= 42 (23.3%)	Later Group (2011-2016) n= 138 (76.7%)		Earlier Group (2006-2011) n= 100 (32.9%)	Later Group (2011-2016) n= 204 (67.1%)	
Age at onset of IBD (mean years ± SD)	39.4 ± 14.9	38.7 ± 12.6	0.253	38.0 ± 11.8	41.4 ± 14.1	0.860
Duration of disease (mo ± SD)	42.4 ± 20.0	13.9 ± 14.9	<0,001	57.9 ± 6.4	32.3 ± 15.7	<0,001
Males, n (%)	28 (66.7%)	88 (63.8)	0.731	52 (52%)	134 (65.7%)	0.021
Hospitalizations	19 (45.2%)	52 (37.7%)	0.380	12 (12%)	25 (12.3%)	0.949
Biological treatment	0	20 (14.5%)	0.009	1 (1%)	1 (0.5%)	N/A
Surgery	10 (23.8%)	13 (9.4%)	0.014	1 (1%)	1 (0.5%)	N/A

N/A: Not applicable

groups in gender for CD patients (33.3% versus 36.2%). On the other hand, in UC gender differences changed significantly and the proportion of males increased in the later group (n= 134, 65.7%) compared to the earlier group (n= 52, 52%) (p=0. 021) (Table 4).

In CD patients there was no statistical difference among the earlier and later groups in disease phenotype. The earlier group includes 10 patients (23.8%) with penetrating phenotype and 32 patients (76.2%) with inflammatory phenotype. During the follow-up period

the disease phenotype had changed in one patient (2.4%) from inflammatory to stenosing phenotype. In the later group, stenosing phenotype was observed in 12 patients (8.7%), penetrating phenotype was observed in 11 patients (8%) and inflammatory phenotype was observed in 115 patients (83.3%). During the follow-up period the disease phenotype had changed in 5 (3.6%) from inflammatory to stenosing (4 patients) and penetrating (1 patient) phenotype.

There was no statistically significant difference between the earlier group and the later group for hospitalizations rates in CD (n=19, 45.2% versus n=52, 37.7%) and UC (n=12, 12% versus n=25, 12.3%). Among CD patients, the proportion of patients receiving biological agents in the later group is 14,5 % (n=20), on the other hand no patient in the earlier group received biological agents (p=0.009). This great difference between the two groups in receiving biological agents shows that there was an increase in the trend of the use of biological agents in the later group. Features for the earlier and later groups for patients with CD and UC are shown in table 4.

The proportion of CD patients undergoing surgery decreased significantly in the later group (n=13, 9.4%) compared to earlier group (n=10, 23.8%) (p < 0.014). In the later CD group, the proportion of female patients who underwent surgical treatment (9, 18%) was greater than the proportion of male patients (4, 4.5%). In contrast, in the earlier CD group the proportion of female patients who underwent surgical treatment (4, 9.5%) was lower than that for male patients (6, 14.3%).

In the CD group the proportion of active smokers was significantly higher in the later group (n= 11, 26.2%) compared to earlier group (n= 58, 42%) (p=0.032). Other variables (Appendectomy, family history, disease localization, upper GI involvement, perianal disease and main extraintestinal manifestations) did not differ between earlier and later groups in CD. In patients with UC the proportion of the biological therapy, surgery and other variables were similar.

Discussion

This single center experience study reports the evaluation of UC and CD in central Turkey. Our data reflects frequency, gender distribution and disease severity (measured by hospitalization, biological therapy and surgery) in a cohort of IBD patients in the Middle East region. To investigate whether the frequency and nature of CD and UC have changed during the study period each disease group was divided into two equal time period subgroups according to the date of diagnosis. The major finding of this study was that the course of IBD in Turkish patients appears to be between that of Europe and Asia. It was observed that among the CD patients, the proportion of patients receiving biologic therapy has increased while the rate of surgery has decreased.

In this study, the occurrence of UC (304, 59.8%) was almost twice as common as that of CD (191, 37.6%),

which is consistent with Asian populations and developing countries (5). The Epidemiologic studies in Asia and Pacific regions have reported that among patients with IBD, UC is the predominant disease and is seen twice as often as CD (4). In our earlier group, UC: CD ratio was approximately 2.5:1 and the distribution of UC and CD in the earlier 5 years period was similar to those of Asia and developing countries (4). It was observed that the proportion of CD has been more prominent in the later group (earlier group 29.6%, later group 40.4%) where the UC: CD ratio was approximately 1.5:1. This finding is compatible with Western countries (2). It has been shown that the incidence of UC has been stable, while the incidence of CD has continually increased in the past 5 decades in western countries (2, 3). However, in the developing countries and Asia, studies have demonstrated that the incidences of both UC and CD have been increasing (2, 4).

In the current study, male gender (62.4%) was more prevalent than female gender (37.6%) among IBD patients. The male: female ratio for UC and CD were 2.38 and 1.47, respectively. Male: female ratio was similar in earlier and later groups among CD patients (2.0 to 1.7, respectively), while there was a significant difference in UC patients (1.0 to 1.9, respectively) (p=0.021). Previous studies revealed that in high-incidence areas UC occurs more frequently in males while CD occurs 20%-30% more frequently in females. On the other hand, in low-incidence areas and Asian countries, male gender domination was reported in patients with UC or CD (2, 4, 17-19). In our study, similar to the Asian population, male predominance was seen in CD and UC patients. However, when we compared the gender distribution in earlier and later groups our results revealed that there was an increasing trend of female predominance in CD, which is compatible with western populations (17-19).

In the literature, complicated phenotypic changes have been associated with longer follow-up periods (20). Inflammatory forms of CD predominate during the first years of disease onset however it has been shown that that the 20-year cumulative rate of all complications is more than 60% and most of the patients with CD experience complications after 40 years of disease onset (2,21). Most of the population-based studies on the progression of CD have been conducted in Western populations. There is limited data on the natural course of IBD in Asia (12). Previous studies from Asian regions have revealed a more favorable clinical disease course of CD than Western regions (2,17,18). In the current study, 18.3% of CD had structuring and/or penetrating complications at diagnosis, which was lower than that of western countries and resembled those of the Asian patterns of CD. This can be explained by ethnic and cultural differences as well as improvements in immunosuppressive and biological treatment (2,7,19). Throughout the follow up period for CD, only six patients (3.6%) experienced complicated phenotypic changes. In the earlier group, only one patient (2.4%) progressed to stenosis, while in the later group,

five patients (3.6%) (4 stenosis, 1 penetration) developed complicated phenotypic behavior.

In the current study, severity of IBD was assessed by the need for hospitalization, biological therapy and surgery. Our study revealed that the rate of patients with severity indicators were significantly higher in CD than those in UC, including hospitalization in (39.4%, 12.2%, respectively), biological therapy (11.1%, 1.0%, respectively), and surgery (12.8%, 0.7%, respectively). Previous studies conducted on Western populations showed a five year surgery rate of 7%-20% for CD and 24% -61% for UC (2,9,22-24). On the other hand, studies conducted on Asia population reported a five years surgery rate of 3% for UC and 9.1%-44% for CD (5,2526). Intestinal resection was more common in our female patients with CD than male patients with CD, which is in accordance with the rates for Western countries, while our overall surgery rates for CD and UC closely resembles those of the Asian patterns of CD (2,19). In the CD group, patients had bowel surgery mostly in the first year of diagnosis. We conducted a subgroup analysis to identify the possible risk factors associated with surgery. There were no significant differences between surgery and non-surgery groups in terms of age at onset of CD, duration of disease, smoking, appendectomy, family history, disease location, combination with upper GI involvement, disease behavior, and perianal disease, extraintestinal manifestation, and steroid dependence. However, we found that the frequency of female gender and the proportion of patients with stenosing and/or penetrating behavior were significantly higher in the surgery group. We compared the earlier and later groups to assess how surgery rates have been affected over the years. The surgery rate in UC patients remained stable and only one patient received surgical intervention in both earlier and later groups. On the other hand, among CD patients, the surgery rate in the earlier group decreased dramatically from 23.8% to 9.4% in the later group. Recent studies have suggested that the increased use of immunosuppressant and biologic therapies may explain the recent fall in first surgery and secondary surgery rates in CD (11,27,28). When we compared the frequency severity indicators in earlier and later groups, despite the fact that the frequency of CD in IBD had increased in the second five years period we observed that the surgery rates decreased and hospitalization rates remained stable, which suggests that as in the Western countries, biological treatment (adalimumab and infliximab) treatment had a positive impact on surgery rates in Turkey.

In our study only one case underwent a secondary bowel resection and this remarkably low rate is similar to results of previous studies from Asia (17-19,29). Moreover we also observed that among CD patients, the biological treatment group showed statistically significant longer duration of disease, higher frequency of female gender, higher rates of appendectomy and

axial joints involvement compared to the non-biological treatment group. Among patients with CD, the proportion of patients receiving biological treatment was higher in the later group compared to the earlier group. However, in the UC group the rate of patients receiving biological treatment was similar in both groups. The proportion of patients with appendectomy, stenosing and penetrating behavior, steroid dependence, and peripheral arthropathy were significantly higher and the duration of disease was longer in the hospitalized group compared to the non-hospitalized group. In patients with both CD and UC, hospitalization rates showed no change in either the earlier or later groups. Despite the increasing frequency of CD and UC, the stable hospitalization rates suggest a positive effect of the immunosuppressive and biological therapy on hospitalization rate. This finding supports the importance of the immunosuppression and biologic agents in our country.

Despite the present report having a single-center and retrospective design we believe that our findings are still important. Firstly our study involved a large number of patients with UC and CD. Secondly, the patients included in the study were followed-up over a long period. Thirdly a subgroup analysis was performed to compare the natural course of IBD patients in two different time periods and to identify the severity indicators for CD and UC.

In conclusion, our results show that the natural course of IBD in Turkish patients appears to be between that of Europe and Asia. In patients with CD, the rate of patients receiving biologic therapy increased, while rate of surgery decreased over the ten-year period. Biological therapy seems to have a positive effect on decreased intestinal resection rates.

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