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A trend analysis of inflammatory bowel disease in non-endemic era (1993-2023)

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ABSTRACT

Aims: In this study, we aimed to evaluate the demographic and epidemiological trends of ulcerative colitis (UC) and Crohn's disease (CD) in non-endemic era for inflammatory bowel disease (IBD) during the past three decades.

Methods: UC and CD patients who had follow-up at least 6 months between June 1993 and February 2023 were evaluated retrospectively. Electronic medical databases, personal queries and IBD registries have all been used to collection data on the clinical and demographic characteristic of all patients.

Results: A total of 1549 adult patients with UC and CD were admitted to study. UC was diagnosed in 873 (56.4%) patients (male 538, 61.6%) and CD was diagnosed in 676 (43.6%) patients (male 404, 59.8%). Median total disease duration was 8.3 years in UC group, as well as 6.8 years in CD group. In patients with UC, proctitis was 154 (17.6%), left sided colitis was 410 (47%) and extensive colitis was 309 (35.4%). In CD patients, ileal involvement was found in 297 (43.9%), colonic in 76 (11.2%), ileo-colonic in 299 (44.2%) and isolated upper gastrointestinal involvement in 4 (0.6%) cases. 529 (78.3%) patients had inflammatory disease (non-stenosing non-penetrating behavior), 45 (6.7%) had stenosing behavior, 102 (15.1%) had penetrating behavior, as well as 196 (29%) patients had perianal disease. Mesalazine 658 (75.4%) and thiopurine 397 (45.5%) were the most frequently used conventional treatments for UC, while thiopurine 304 (45%) was most commonly used for CD patients. In the last two-decade, proportion of the biologic usage were 27.9% and 32.1% in UC patients 28.5% and 31.4% in CD patients respectively. Over the three decades, abdominal surgery was 49.2%, 27.8% and 36.3% in CD and colectomy rates was 2.0%, 2.7% and 3.7% in UC patients.

While the rate of UC patients has slightly decreased to 98 (61.6%), 401 (58.5%) and 374 (53%) frequency of CD patients has increased to 61 (38.4%), 284 (41.5%) and 331 (47%). Over the course of three decades, there were more UC patients than CD patients, however proportion of UC/CD has been continuously decreased (1.61, 1.41 and 1.13) for three decades respectively.

Conclusion: Our study showed that the frequency of UC and CD has significantly increased during the previous three decades in non-endemic era for IBD. While the frequency of UC patients has slightly decreased, that of CD patients has steadily increased over the past three decades. Although the use of biologics has significantly increased, proportions of the major abdominal surgeries and colectomies has not prominently changed.

Keywords: Inflammatory bowel disease, ulcerative colitis, crohn's disease, three decades

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation and includes ulcerative colitis (UC) and Crohn's disease (CD).[1] It has a progressive and relapsing nature of that limits the quality of life and affects disability-adjusted life years (DALYs). Furthermore, instead of completely curing the disease, treatment aims to limit inflammation, relieve symptoms, and prevent disease progression. As a consequence, many patients experience the need for surgical treatment and various complications.[2,3] Studies have shown that due to the nature of the disease, early diagnosis and effective treatment play a key role in controlling the disease. Considering the availability of newly developed biological agents and new treatment strategies, it is now more possible to stop the progression of the disease. Considering that the disease is triggered by environmental factors as well as genetic factors and that its incidence is increasing in developing

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countries, determining the prevalence of the disease in our region may be beneficial in organizing early diagnosis screening programs.[4-7]

It was reported that 4.9 million people were affected by IBD worldwide in 2019, with the highest prevalence of the disease in Scandinavian countries, North America, and Oceania [8]. Recently, studies analyzing trends in the epidemiology of the disease and its future perspective in countries with high prevalence have been reported. So far, limited data exist regarding the changing epidemiological trends in emerging nations experiencing rapid industrialization such as the Middle East and Turkiye. The development of novel strategies for disease screening, monitoring, and treatment management as well as the development of appropriate strategies by healthcare providers will be made feasible by the demographic analysis of the disease and the detection of shifts in its epidemiology.

The purpose of this study was to assess the epidemiological and demographic trends of UC and CD during the previous three decades in the non-endemic era of IBD.

METHODS

Participants in the study had to be older than 18 years old, diagnosed or confirmed in our clinic between June 1993 and February 2023, and followed up at least six months. The current analysis included patients from different regions who presented to a tertiary center in Ankara. Patients with insufficient info, follow-up periods shorter than six months, and cases of indeterminate colitis were not included in the analysis. Methodologies were carried out by the 1964 Helsinki Declaration, its subsequent revisions, the institutional research committee's ethical guidelines, or comparable criteria. This study was approved by the Ankara Bilkent City Hospital Ethics Committee (Date: 25.01.2023, Decision No: E1-23-3218). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Relevant data included demographic details of patients, disease diagnoses and subtypes, laboratory variables at diagnosis, treatment details, and clinical outcomes. Before 2009, patients' follow-up documents provided the data, while after 2009, the civil medical record system provided the data. Annual inflammatory bowel disease (IBD) diagnosis data were presented by disease type (UC and CD), age group, and gender.

Patients were divided into three groups depending on the decade of diagnosis, as well as two groups, UC and CD. The current Montreal categorization was used to determine the disease's diagnosis, location, and other characteristics. Before the year 2007, when biological treatments were first introduced, the treatment regimen consisted of immunomodulators, steroids, and mesalazine compounds. If medical treatment was not effective, surgery was performed. In scenarios when prior treatments were not effective, TNF-alpha blockers were the pre-surgical therapy option available after 2007. Other biological agents have been introduced to the treatment regimen as get closer to the present.

The frequency of IBD was defined as the number of patients diagnosed per decade. Age at onset of IBD refers to the date of definitive diagnosis, regardless of the phenotype of the disease, and total disease duration refers to the time between the first diagnosis and the last clinical visit. Family history of IBD is a history of CD or UC in a first- or second-degree relative, self-reported by the study subject. Characteristics of disease covered disease extent (Montreal classifications [9] L1, L2, L3, and L4 for CD; E1, E2, and E3 for UC), behavior (B1, B2, and B3), perianal disease, extraintestinal manifestations (EIMs), or history of bowel resection. Total colectomy refers to CD and UC patients while resective surgery was defined as small-bowel or large-bowel resections for CD patients.

Statistical Analysis

We used IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) for statistical analysis and Microsoft Excel 2013 for graphs. The normality of the distribution of continuous variables was analyzed by using Kolmogorov-Smirnov test. Continuous variables were described as median (1st quartile-3rd quartile). Categorical variables were expressed as frequency (percentage). We compared the frequencies of UC and CD by decades via the Chi-Square test. A p-value < 0.05 was considered significant.

RESULTS

A total of 1549 patients were included in the study; 873 (56.4%) with ulcerative colitis (61.6% male), and 676 (43.6%) with Crohn's disease (59.8% male). The median age at the onset of the disease was the same in both diseases 38 years (28-50). During the 3-decade follow-up, 229 (33.9%) CD patients underwent resective surgery, while 27 (3.1%) UC patients underwent total colectomy. When the frequency of the disease was evaluated, in UC patients, left-sided colitis was 410 (47%), extensive colitis was 309 (35.4%), and proctitis was 154 (17.6%), while in CD patients, ileocolonic involvement (L3) was found in 299 (44.2%), ileal involvement (L1) was found in 297 (43.9%), colonic involvement (L2) in 76 (11.2%), and isolated upper gastrointestinal involvement (L4) in 4 (0.6%). The disease behavior of CD patients was as follows: 102 (15.1%) had penetrating, 45 (6.7%) had stenosing, as well as 196 (29%) patients had perianal disease. Mesalazine compounds 658 (75.4%) and thiopurine 397 (45.5%) were the most frequently used conventional treatments for UC, while thiopurine 304 (45%) for CD patients (Table 1).

While the ratio of UC patients among IBD patients has slightly decreased from 98 (61.6%) to 401 (58.5%) and 374 (53%), the frequency of CD patients increased statistically significantly in the last two decades compared to the first decade [61 (38.4%) in the first decade, 284 (41.5%) in the second decade and 331 (47%) in the third decade, p=0.044] (Figure 1). The proportion of UC/CD has been continuously decreased (1.61, 1.41 and 1.13) for three decades respectively (Table 2). In the last two-decade, proportion of the biologic usage were 27.9% and 32.1% in UC patients 28.5% and 31.4% in CD patients respectively. Over the three decades, abdominal surgery was 49.2%, 27.8% and 36.3% in CD and colectomy rates was 2.0%, 2.7% and 3.7% in UC patients (Table 1).

Table 1. Demographics, clinical, and laboratory data of IBD patients from 1993 to 2023

	UC patients				CD patients			
	1993-2022 (n=873)	**1993-2002 (n=98)**	**2003-2012 (n=401)**	**2013-2022 (n=374)**	**1993-2022 (n=676)**	**1993-2002 (n=61)**	**2003-2012 (n=284)**	**2013-2022 (n=331)**
Age at onset of IBD, years	38 (28-50)	36 (26-49.5)	39 (29.5-50)	37 (27-50)	38 (28-50)	37 (28.5-57)	38 (29-50.75)	38 (28-49)
Gender, male	538 (61.6%)	60 (61.2%)	256 (63.8%)	222 (59.4%)	404 (59.8%)	30 (49.2%)	168 (59.2%)	206 (62.2%)
Smokers (current/Ex)	177 (20.3%) /281 (32.2%)	21 (21.4%) /27 (27.6%)	76 (19%) /135 (33.7%)	80 (21.4%) /119 (31.8%)	255 (37.7%) /168 (24.9%)	23 (37.7%) /11 (18%)	111 (39.1%) /69 (24.3%)	121 (36.6%) /88 (26.6%)
Family history of IBD	148 (17%)	23 (23.5%)	63 (15.7%)	62 (16.6%)	94 (13.9%)	6 (9.8%)	34 (12%)	54 (16.3%)
Appendectomy	15 (1.7%)	1 (1%)	9 (2.2%)	5 (1.3%)	78 (11.5%)	9 (14.8%)	27 (9.5%)	42 (12.7%)
BMI (kg/m^2)	24.61 (21.79-27.76)	25.65 (23.34-28.52)	24.84 (22.37-28.8)	24.38 (21.48-27.41)	24.92 (22.36-28.4)	26 (23.5-28.5)	25.69 (22.5-28.79)	24.61 (22.1-27.76)
Total disease duration, months	99.53 (46.45-152.26)	266.28 (236.65-303.80)	128.93 (95.47-161.33)	55.25 (26.78-84.46)	82.05 (41.43-141.15)	253.23 (219.63-292.58)	217.47 (80.93-167.29)	48.8 (24.47-75.1)
Major abdominal surgery								
Total colectomy	27 (3.1%)	2 (2%)	11 (2.7%)	14 (3.7%)	-	-	-	-
Resective surgery	-	-	-	-	229 (33.9%)	30 (49.2%)	79 (27.8%)	120 (36.3%)
UC (disease extension)								
Proctitis	154 (17.6%)	18 (18.4%)	70 (17.5%)	66 (17.6%)	-	-	-	-
Left-sided colitis	410 (47%)	46 (46.9%)	191 (47.6%)	173 (46.3%)	-	-	-	-
Extensive colitis	309 (35.4%)	34 (34.7%)	140 (34.9%)	135 (36.1%)	-	-	-	-
CD (disease location)								
Ileal (L1)	-	-	-	-	297 (43.9%)	28 (45.9%)	114 (40.1%)	155 (46.8%)
Colonic (L2)	-	-	-	-	76 (11.2%)	6 (9.8%)	33 (11.6%)	37 (11.2%)
Ileo-colonic (L3)	-	-	-	-	299 (44.2%)	26 (42.6%)	136 (47.9%)	137 (41.4%)
Upper gastrointestinal disease (L4)	-	-	-	-	4 (0.6%)	1 (1.6%)	1 (0.4%)	2 (0.6%)
CD (disease behavior)								
Inflammatory disease (B1)	-	-	-	-	529 (78.3%)	47 (77%)	233 (82%)	249 (75.2%)
Stenosing (B2)	-	-	-	-	45 (6.7%)	4 (6.6%)	18 (6.3%)	23 (6.9%)
Penetrating (B3)	-	-	-	-	102 (15.1%)	10 (16.4%)	33 (11.6%)	59 (17.8%)
CD p (perianal disease)	-	-	-	-	193 (28.6%)	12 (19.7%)	85 (29.9%)	96 (29%)
Isolated perianal disease	-	-	-	-	3 (0.4%)	-	2 (0.7%)	1 (0.3%)
Extra-intestinal manifestations	454 (52%)	64 (65.3%)	199 (49.6%)	201 (53.7%)	383 (56.6%)	32 (52.4%)	172 (60.5%)	179 (54%)
Prior conventional medications								
Mesalazine oral	658 (75.4%)	78 (79.6%)	301 (75.1%)	279 (74.6%)	490 (72.5%)	45 (73.8%)	201 (70.8%)	244 (73.7%)
Mesalazine enema	392 (44.9%)	43 (43.9%)	180 (44.9%)	169 (45.2%)	277 (41%)	25 (41%)	123 (43.3%)	129 (39%)
Mesalazine suppository	102 (11.7%)	9 (9.2%)	50 (12.5%)	43 (11.5%)	82 (12.1%)	7 (11.5%)	28 (9.9%)	47 (14.2%)
Sulfasalazine	81 (9.3%)	12 (12.2%)	37 (9.2%)	32 (8.6%)	61 (9%)	5 (8.2%)	21 (7.4%)	35 (10.6%)
Budesonide	115 (13.2%)	15 (15.3%)	46 (11.5%)	54 (14.4%)	80 (11.8%)	7 (11.5%)	32 (11.3%)	41 (12.4%)
Steroids	380 (43.5%)	49 (50%)	169 (42.1%)	162 (43.3%)	291 (43%)	28 (45.9%)	115 (40.5%)	148 (44.7%)
Thiopurine	397 (45.5%)	56 (57.1%)	176 (43.9%)	165 (44.1%)	304 (45%)	25 (41%)	124 (43.7%)	155 (46.8%)
Methotrexate	106 (12.1%)	18 (18.4%)	43 (10.7%)	45 (12%)	62 (9.2%)	8 (13.1%)	23 (8.1%)	31 (9.4%)
Prior biologic medications	278 (31.8%)	46 (46.9%)	112 (27.9%)	120 (32.1%)	201 (29.7%)	16 (26.2%)	81 (28.5%)	104 (31.4%)
Baseline CRP (mg/L)	3.7 (1-10.2)	2.6 (1-10.3)	6.78 (2.37-19.95)	1.72 (0.75-5.3)	6.6 (2.28-19.23)	6 (1-39.2)	7.2 (2.8-21.38)	5.8 (2-14.15)
Baseline HB (g/dL)	13.7 (12.3-14.7)	14.9 (12.7-15.1)	13.7 (11.75-14.6)	13.9 (12.1-14.6)	13 (11.7-14.55)	12.4 (10.8-13.8)	13 (11.38-14.53)	13.5 (12.1-14.7)
Baseline albumin (g/dL)	4.4 (4.2-4.7)	4.5 (4.3-4.9)	4.4 (4.2-4.6)	4.4 (4.1-4.7)	4.2 (3.9-4.5)	4 (3.4-4.7)	4.2 (3.98-4.5)	4.2 (3.9-4.5)
Baseline CDAI (CD)	-	-	-	-	305.5 (214.5-395)	345 (245-455)	291 (204.75-385.5)	307 (212-385)
Baseline partial MAYO score (UC)	6 (5-7)	6.5 (4.75-7)	7 (5-7)	5 (5-7)	-	-	-	-

Variables are summarized by median (1st quartile-3rd quartile) and frequency (%), UC: Ulcerative colitis, CD: Crohn's disease, IBD: Inflammatory bowel disease, BMI: Body-mass index, CRP: C-reactive protein, HB: Hemoglobin, CDAI: Crohn's disease activity index, Extraintestinal manifestations: Peripheral arthralgia + Peripheral arthritis + Ankylosing spondylitis + Sacroiliitis + Erythema nodosum + Pyoderma gangrenous + Apthous ulcer + Uveitis + Episcleritis + Primary Sclerosing Cholangitis, Prior biologic medications: Adalimumab + Infliksimab + Vedolizumab + Ustekinumab + Certolizumab

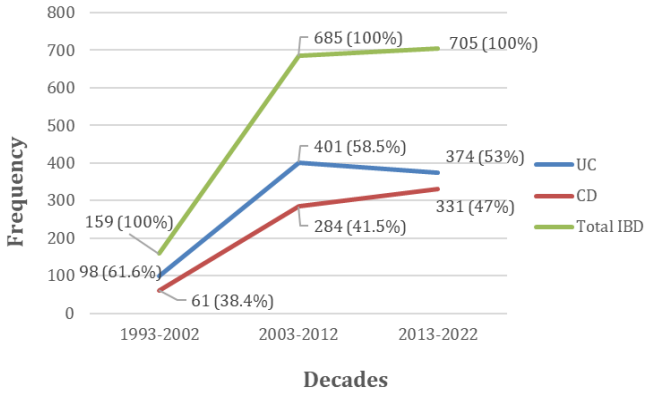

Figure 1. Trend analysis of patients diagnosed with UC, CD, and Total IBD by decade subgroups

Variables are summarized frequency (%), IBD: Inflammatory bowel Disease, CD: Crohn's disease, UC: Ulcerative colitis

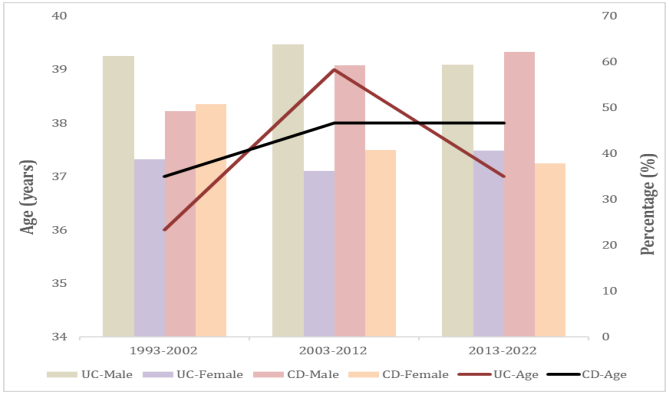

Figure 2. Frequency of CD and UC adjusted by age and gender on decades (1993-2022)

UC: Ulcerative colitis, CD: Crohn's disease

Table 2. Comparisons and data of UC, CD, and Total IBD by decade subgroups

	Total IBD	UC	CD	UC/CD	p value
Decades					0.044
1993-2002	159 (10.3%)	98 (61.6%)	61 (38.4%)	1.61	
2003-2012	685 (44.2%)	401 (58.5%)	284 (41.5%)	1.41	
2013-2022	705 (45.5%)	374 (53%)	331 (47%)	1.13	
1993-2022	1549 (100%)	873 (56.4%)	676 (43.6%)	1.29	

Variables are summarized frequency (%), UC: Ulcerative colitis, CD: Crohn's disease, IBD: Inflammatory bowel disease

The frequency of CD patients tended to rise over time [61 (38.4%), 284 (41.5%), and 331 (47%) through the first to the last decade, respectively, p=0.044], despite the incidence of UC patients slightly decreasing [98 (61.6%), 401 (58.5%) and 374 (53%) through the first to the last decade, respectively]. Over the previous three decades, the UC/CD ratio has gradually decreased (1.61, 1.41, and 1.13, respectively). Biologic therapy over the past 20 years was 28.5% and 31.4% for CD patients and 27.9% and 32.1% for UC patients, respectively. Over the last three decades, the percentage of CD patients who had abdominal surgery was 49.2%, 27.8%, and 36.3%, whereas the percentage of UC patients who had a colectomy was 2.0%, 2.7%, and 3.7%, respectively (Table 1).

Between the three decades, the median age at onset of UC was 36 years (26-49.5), 39 (29.5-50), and 37 (27-50), respectively, according to decades. The median age at onset of CD was 37 years (28.5-57), 38 (29-50.75), and 38 (28-49), respectively, similar to UC. There was no statistically significant difference regarding the first diagnosis of both diseases (p>0.05 for all parameters). Gender distribution over decades was statistically similar in both diseases (p>0.05 for all parameters). Both CD and UC were diagnosed more frequently in males (59.8% and 61.6%, respectively (Figure 2).

DISCUSSION

Since the second half of the twentieth century, IBD has become more common. It continues to grow day by day. As the IBD population ages over the next ten years, physicians will have to deal with an increasing number of patients with IBD and more challenging management. Geographical variations in the disease's prevalence are due to both hereditary and environmental factors. Each region has different clinical presentations, disease involvement, complications, and surgery rates.[10,11] The epidemiology of IBD in developed countries and regional variations in phenotype have been demonstrated by recent investigations. There is little evidence of the disease's prevalence and other distinguishing characteristics in developing countries. It is predicted that the prevalence of IBD will increase annually until 2050 worldwide.[10] Establishing the disease phenotype and epidemiology based on geographic regions is essential for developing the most appropriate strategies for healthcare management, given the rising prevalence of the disease and its regional variations.

In developed territories like countries in North America, Europe, and Oceania, the incidence of IBD has been rising since the 1950s but has stabilized in the last 20 years.[12-14] In Canada, the incidence of IBD was estimated to be 29.9 per 100,000 people in 2023, and was predicted to be 31.2 per 100,000 people in 2035 according to utilizing data. It has been claimed that the incidence will be higher in the pediatric population, even though the incidence rate in adults is expected to increase considerably.[15] This was explained by the way that the etiology of the disease is affected differently depending on an individual's age. Smoking has a greater effect on the disease's etiology in people over the age of 40, and the role of NOD-2 genetic mutations in younger people. The lower incidence of IBD in adults compared to the pediatric population was associated with a decrease in smoking rates in Canada. In our study, the median age of onset of disease in the adult age group was 38 for both diseases, and no difference was observed across decades. Since the analysis did not include the pediatric age group, a comparison of pediatric and adult age group frequencies could not be made.

In developing countries, incidence rates remained relatively low compared to developed countries until the late 20th century.[16,17] This phenomenon is complex and may be attributed to environmental and ethnic influences, suggesting that individuals in higher socioeconomic settings have fewer childhood infectious agents, less antibiotic exposure, and a different diet. In particular, a Western diet may play an important role in gut microbial dysbiosis, which is believed to be one of the main risk factors for IBD.[18,19] Since the

2000s, an increase in the epidemiology of IBD has begun to attract attention in developing countries. The incidence is increasing with industrialization and Western-type dietary habits. Furthermore, there is a correlation between increased complications in IBD patients challenges in obtaining healthcare, and insufficient therapy.[16] Compared to developed countries, developing countries have a greater burden.

A systematic review of the last 50 years[20] reported that there was no conclusive evidence supporting a consistent global trend of increasing incidence rates for UC over time. Despite certain countries may show an increasing trend in incidence rates, this was explained by the inclusion of studies from a wider range of countries and the strong association between geographic location and UC incidence rates. In contrast to UC, there is a modest increase in the incidence of CD. The prevalence of CD seems to be higher in urban areas than in rural areas, and also higher in socioeconomic classes. The current study found a marked increase in the frequency of IBD over the last two decades compared to the first decade.

There was no significant change in the prevalence of IBD last two decades. When CD and UC were assessed separately, it was shown that the incidence of CD slightly rose (41.5% vs. 47%, respectively) while the incidence of UC slightly decreased (58.5% vs. 53%, respectively) in this study. UC first appeared in developed countries, followed by CD, and in regards to incidence rates, CD has mostly surpassed UC throughout the last two decades. However, UC tends to be more prevalent than CD in developing countries.[21] Our analysis showed that although the frequency of UC was higher, the frequency of patients with CD started to increase in the last two decades. The proportion of UC/CD has continuously decreased (1.61, 1.41, and 1.13) for three decades respectively. This raises the possibility that the frequency of CD may be higher than the incidence of UC in Turkiye in the future, as in developed countries.

Previous studies have shown that in Western populations, the prevalence of CD tends to be greater in women than in men, while the opposite trend is observed in Asia. However, several studies have highlighted gender differences and variability in IBD prevalence.[22,23] In familial cases of IBD, a female predominance appears to be more pronounced than in sporadic cases.[24] In the present study, the majority of patients with IBD were male.

Limitations

The study had several limitations. First, the accuracy of the estimated burden of IBD largely depends on the availability and quality of the data collected. There may be bias in the epidemiological data as cases with missing data were excluded from the study. Second, the obtained data could not be generalizable due to the being collected from a single center. The fact that the patients had a long follow-up period, patient data were consistently collected at each visit, and experienced IBD gastroenterologists conducted the disease diagnosis and therapy were the study's merits.

CONCLUSION

The current analysis showed that although the UC incidence is higher, the UC/CD ratio has been decreasing over the last 2 decades. In our country, the incidence of inflammatory bowel disease is increasing, similar to how it is globally.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital Ethics Committee (Date: 25.01.2023, Decision No: E1-23-3218).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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