

Inflammatory bowel disease in Transylvania region- findings from a tertiary care center in Romania

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Abstract. Background: The aim of the study is to determine the clinical and demographic parameters of inflammatory bowel disease (IBD) patients in a tertiary care center from Transylvania, Romania. Methods: We included in the study IBD patients admitted between 1 January 2016 and 1 January 2018 in the Institute of Gastroenterology and Hepatology, Cluj-Napoca, Transylvania region, Romania. Demographic and clinical features collected from the medical records were studied. Results: A total of 220 IBD patients were included, 165 (75%) with ulcerative colitis (UC), 55 (25%) with Crohn’s disease (CD). Mean age at diagnosis was 39.49 years. The male to female ratio was 1.17:1 in UC group and 1:1.75 in CD group. Both groups revealed the predominance of urban residence (69.09% in UC group, 74.55% in CD group, $p=0.443$). A history of smoking was observed in 63.64% of CD patients and in 47.28% of UC patients. In CD group, the most frequent disease location was small intestine, and the most frequent behavior was non-stricturing non-penetrating. In the UC patient cohort, 21.21% had proctitis, 51.51% left-sided colitis, 27.28% extended colitis. Clostridium difficile infection affected 3% of the patients in the UC group and none in the CD group. Intestinal complications occurred in 6.06% of the UC patients and 50.91% of the CD patients ($p<0.001$). Extraintestinal complications were more common in the CD group (32.73%) than in the UC group (13.33%) - $p=0.001$, with arthropathy and erythema nodosum being the most frequent. 38.2% of CD patients and 9.6% of UC patients underwent surgery for disease related complications. Conclusion: The demographic pattern is like the one described previously in Western Europe. These diseases tend to cluster among urban communities affecting young individuals with higher education level. The clinical course is different, with lower rates of intestinal and extraintestinal complications and lower need for surgery.

Key Words: ulcerative colitis, Crohn’s disease, IBD epidemiology, IBD surgery.

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Introduction

Inflammatory bowel disease, ulcerative colitis, Crohn’s disease, and indeterminate colitis are inflammatory disorders with an unpredictable evolution marked by flare-ups and periods of remission, being extremely common in developed, industrialized countries (Hanauer et al 2006).

These diseases are common in Western countries, with a growing incidence since 1950. In contrast, until the last decade, low incidence and prevalence rates have been reported in other parts of the world, such as Eastern Europe, South America, Asia, and Pacific region. There is a recent trend of change in the epidemiology of these diseases with increasing incidence in areas with low incidence, while in Western Europe and North America the incidence is somewhat stable, with lower incidence rate of ulcerative colitis (Lakatos et al 2006).

Increasing incidence rates reported in Eastern European countries may be the result of the methodology used in previous studies (mostly retrospective studies), increased suspicion for this pathology, differences in the diagnostic methods used or may represent a real increase in incidence (Burisch et al 2013). There are several reasons for the increasing incidence rates in developing countries and the economic development with life-style changes is only one of them (Bernstein et al 2010).

There are few epidemiological data on inflammatory diseases in Eastern European countries, especially in Romania. Therefore, the aim of this paper is to provide epidemiological and clinical information about patients with inflammatory bowel disease in Transylvania, a region in the northwestern part of Romania, admitted in our clinic between January 2016 and January 2018.

Material and method

This prospective study was conducted in the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, tertiary referral center located in the northwestern part of Romania, with increased addressability from all the regions of the country. The study was approved by the local ethics committee of the Institute. Patients were prospectively included in the study between 1 January 2016 and 1 January 2018.

The diagnosis of inflammatory bowel disease was established on the basis of previously published clinical, radiological, endoscopic and histological criteria (Lennard- Jones et al 1989). Demographic and clinical data were obtained by patient interview after written informed consent and from their medical records. The following data were noted: demographic characteristics, age at diagnosis, clinical presentation, location and severity of disease, presence of intestinal complications and extraintestinal manifestations, therapeutic modalities and type of therapy

and indications for surgery. The diagnosis delay was defined as the time between onset of symptoms and the time of diagnosis. Extent of the disease in patients with ulcerative colitis was classified as: proctitis- disease affecting only the rectum (E1), left-sided colitis (E2), extended left-sided colitis (E3), according to the Montreal classification (Satsangi et al 2006) and was established by using total colonoscopy (88% of cases) or imaging tests (ultrasonography, computer tomography) in cases of severe colitis. Crohn's disease was classified according to Montreal classification, including age at diagnosis (A1 <17 years of age; A2: 17-40 years of age; A3 >40 years of age), sites of gastrointestinal involvement (L1-ileal, L2-colonic, L3-ileocolic) and disease pattern (B1- non-stricturing non-penetrating, B2-stricturing, B3-penetrating, p-perianal disease) (Satsangi et al 2006). Disease severity was classified clinically according to Truelove and Witts' criteria as mild, moderate and severe (Truelove et al 1955). Crohn's disease activity were classified according to CDAI (Crohn's Disease Activity Index) in: remission(<150), mild(150-200), moderate(200-450), severe form(>450) (Best et al, 1976).

Statistical analysis was performed using SPSS for Windows (version 20, Chicago, IL, USA). Nominal variables were described by using frequencies. Patient groups were compared using the one-way analysis of variance (ANOVA), as well as Pearson Chi-Square or Fisher's exact test. Quantitative variables were characterized as mean + standard deviation or as median and percentiles (25-75%) and were compared using the student's t-test or Mann-Whitney tests. The level of statistical significance was established when $p < 0.05$.

Results

Demographic characteristics

During the study period, a total of 244 potential IBD patients were recruited. Five patients were diagnosed with infectious colitis and excluded from the study. Twelve patients had terminal ileitis and segmentary colitis without complete criteria for Crohn's disease and were excluded from the study. 227 patients were identified with IBD, 165 with ulcerative colitis (72.69%), 55 with Crohn's disease (24.23%) and 7 patients with indeterminate colitis (3.08%). Due to the small size of the indeterminate colitis group, only ulcerative colitis and Crohn's disease patients were analyzed.

Sixty-two patients (37.57%) in the ulcerative colitis group and 28 (50.9%) patients in the Crohn's disease group were newly diagnosed. Median diagnosis delay was 2 (1; 3) months in patients with UC and higher in CD patients, 5(2; 12) months ($p=0.000$). Median disease duration was 2 (0;5.5) years in UC and 2 (0; 4) years in CD ($p=0.539$).

The mean age of patients studied was 43.28 (range 18-76). Patients with Crohn's disease were diagnosed at a younger age (36.98 + 14.45 years of age) than those with ulcerative colitis (40.18 + 13.92 years of age), $p=0.145$. Preponderance of women was observed in patients with Crohn's disease (men/women = 1:1.75) and that of men in those with ulcerative colitis (men/women = 1.17:1), $p=0.024$.

The discontinuation of the activity due to intestinal pathology was described in 36.97% of the patients with ulcerative colitis and in 54.54% of those with Crohn's disease. The environment was predominantly urban in both pathologies (69.09% in patients

with ulcerative colitis, 74.55% in those with Crohn's disease). Romanian ethnicity was predominant (85.45% of the patients with inflammatory bowel disease), followed by Hungarians (13.18%), other ethnic groups (Bulgarian, Roma, Ukrainian) being present in very low proportions (0.45%). Four patients (2.4%) in ulcerative colitis group had a first degree relative with inflammatory bowel disease (Table 1).

Regarding associated pathologies, appendectomy is more common in patients with Crohn's disease than in those with ulcerative colitis (38.18% versus 7.88%, $p=0.000$). Tonsillectomy and adenoidectomy are more common in patients with Crohn's disease (18.18% and 5.45%) than in those with ulcerative colitis (7.27% and 4.85%). The association with autoimmune diseases is more common in patients with Crohn's disease (9.09% vs. 3.03%) - $p:0.062$.

Among patients with Crohn's disease, 50% were smokers at the time of diagnosis, while 52.73% of patients with ulcerative colitis never smoked and 37.58% were former smokers ($p=0.000$). NSAIDs are commonly consumed at a rate of 36.15 in UC and 38.88 in CD, 19.88% and 16.67% of patients with UC and CD, respectively, had used these drugs in the past. 70.91% of patients with ulcerative colitis and 52.73% of those with Crohn's disease were breastfed(exclusive) for at least 6 months (Table 2).

Disease characteristics

Clinical presentation

Ulcerative colitis group

The most frequent was left-sided colitis (51.51%), followed by extended colitis (27.28%), proctitis being present in only 21.21% of cases. The predominant symptoms were: diarrhea (72.12%) and rectal bleeding (88.48%), abdominal pain (12%), weight loss (4.5%), fever (1.2%). When included in the study, 15.15% of patients were in remission, while 37.58% had mild flare-ups, and 26.67%, 20.61% respectively, had moderate or severe flare-ups. Intestinal complications occurred in 6.06% of cases, the most common being represented by toxic megacolon (3.64%) (Table 3).

Extraintestinal manifestations were present in 13.3% of patients with ulcerative colitis, 10.3% had only one manifestation and 2.4% had two extraintestinal manifestations. In patients with UC, arthritis was the most frequent (4.85%). Thromboembolic complications occurred in 5.4% of cases, mostly represented by deep vein thrombosis (Table 5).

Throughout the study, Clostridium difficile infection has complicated the evolution of patients with ulcerative colitis in only 3% of cases. Colon cancer occurred in only 3 of the cases of ulcerative colitis, 1 localized in the descending colon, 2 localized in the sigmoid colon, after a time period of 11, 13 and 16 years respectively.

Management of the UC

In the study period only 3 patients with ulcerative colitis were on anti TNF alpha therapy, while 101 patients (63%) were on maintenance treatment with oral 5-aminosalicylates and 46 patients (27.87%) with 5-aminosalicylates and azathioprine.

In the ulcerative colitis group, 16 patients (9.6%) required surgery for complications due to illness severity or lack of response to treatment (total proctocolectomy with end ileostomy: 3, total colectomy with ileostomy: 13). Indications for surgery

Table 1. Demographic characteristics of the study population

Variable	Total IBD Number of patients (%)	UC Number of patients (%)	CD Number of patients (%)	P OR(CI95%)
Age at diagnosis				
<40 years	120(45.55%)	83(50.30%)	37(67.27%)	p= 0.029 OR:0.492 (0.259-0.934)
≥40 years	100(45.45%)	82(49.70%)	18(32.73%)	
Gender				
Male	109(49.55%)	89(53.94%)	20(36.36%)	p=0.024 OR:2.049(1.093-3.844)
Female	111(50.45%)	76(46.06%)	35(63.64%)	
Ethnicity				
Romanian	188(85.45%)	141(85.45%)	47(85.45%)	p= 0.451
Hungarian	29(13.18%)	22(13.33%)	7(12.73%)	
Bulgarian	1(0.45%)	1(0.61%)	0	
Roma	1(0.45%)	0	1(1.82%)	
Ukrainian	1(0.45%)	1(0.61%)	0	
Education level				
Basic	87(39.55%)	62(37.58%)	25(45.45%)	p=0.301 OR:1.384(0.747-2.566)
Higher	133(60.45%)	103(62.42%)	30(54.55%)	
Residence				
Rural	65(29.55%)	51(30.91%)	14(25.45%)	p=0.443 OR:1.310(0.657-2.614)
Urban	155(70.45%)	114(69.09%)	41(74.55%)	
Marital status				
Married	167(75.90%)	132(80%)	35(63.64%)	p=0.014 OR: 0.438 (0.224-0.854)
Single	53(24.10%)	33(20%)	20(36.36%)	
First degree relative with IBD	4 (1.815)	4(2.42%)	0(0.00%)	p=0.574 OR:0.976(0.953-1.0)

Table 2. IBD risk factors and associated diseases

Variable	Total IBD Number of patients (%)	UC Number of patients (%)	CD Number of patients (%)	p OR(CI95%)
Smoking				
Nonsmoker	107(48.64%)	87(52.73%)	20(36.36%)	p<0.001
Smoker	34(15.45%)	16(9.70%)	18(32.73%)	
Former smoker	79(35.91%)	62(37.58%)	17(30.91%)	
NSAIDS				
Never	97(44.09%)	73(43.97%)	24(44.45%)	p= 0.858
Current	81(36.81%)	60(36.15%)	21(38.88%)	
Past	42(19.09%)	33(19.88%)	9(16.67%)	
Breastfeeding (at least 6 months)	146(66.36%)	117(70.91%)	29(52.73%)	p= 0.013 OR:0.458(0.244-0.857)
Autoimmune diseases	10(4.54%)	5(3.03%)	5(9.09%)	p=0.062 OR:3.2(0.890-11.505)
Allergies	41(18.63%)	29(17.58%)	12(21.82%)	p= 0.484 OR:1.309(0.615- 2.785)
Appendectomy	34(15.45%)	13 (7.88%)	21 (38.18%)	p= 0.000 OR:7.222(3.293 – 15.838)
Tonsillectomy	22(10%)	12 (7.27%)	10 (18.18%)	p= 0.02 OR:2.833(1.149- 6.987)
Adenoidectomy	11(5%)	8 (4.85%)	3 (5.45%)	p= 1.000 OR:1.132 (0.290 – 4.427)

Table 3. Ulcerative colitis- extent of the disease

Variable	Number of patients (%)
E1- proctitis	35(21.21%)
E2- left-sided colitis	85(51.51%)
E3- extended colitis	45(27.28%)

Table 4. Intestinal and extraintestinal complications

Variable	Total IBD	UC	CD	P OR(CI 95%)
Intestinal complications	38(17.27%)	10(6.06%)	28(50.91%)	p<0.001 OR: 16.074(7.011-36.852)
Intestinal obstruction	13(5.91%)	1(0.61%)	12(21.82%)	P=0.000 OR:45.767(5.790-361.774)
Internal fistulae	13(5.91%)	0(0.00)	13(23.64%)	p=0.000
Toxic megacolon	6(2.73%)	6(3.64%)	0(0.00)	p=0.341
Perforation	1(0.45%)	1(0.61%)	0(0.00)	p=1.000
Abscess	10(4.55%)	0(00)	10(18.18%)	p<0.001
Neoplasia	4(1.82%)	3(1.82%)	1(1.85%)	p=1.000 OR: 1.000(0.102-9.816)
Extraintestinal complications	40(18.18%)	22(13.33%)	18(32.73%)	p= 0.001 OR: 3.162(1.539-6.498)
Arthritis	19(8.64%)	8(4.85%)	11(20%)	p= 0.001 OR: 4.906(1.860-12.944)
Ankylosing spondylitis	10(4.55%)	5(3.03%)	5(9.09%)	p= 0.126 OR: 3.200(0.890-11.505)
Erythema nodosum	9(4.09%)	5(3.03%)	4(7.27%)	p= 0.232 OR: 2.510(0.649-9.701)
Uveitis	3(1.36%)	0(0.00)	3(5.45%)	p=0.015
Episcleritis	2(0.91%)	0(0.00)	2(3.64%)	p=0.062
Primary sclerosing cholangitis	2(0.91%)	1(0.61%)	1(1.82%)	p= 0.438 OR: 3.037(0.187-49.387)
Pyoderma gangrenosum	5(2.27%)	4(2.42%)	1(1.82%)	p= 1.000 OR: 0.745(0.082-6.814)

Table 5: Crohn's disease- disease characteristics according to the Montreal classification

Characteristics	Number of patients (%)
Age at the diagnosis (years)	
A1: <17	1 (1.82%)
A2: 17-40	39(70.91%)
A3: >40	15(27.27%)
Disease location	
L1: Ileum	15(27.27%)
L2: Colon	17(30.91%)
L3: Ileocolic involvement	17(30.91%)
L4: Isolated upper disease	2(3.63%)
Disease behavior	
B1: Non-stricturing, non-penetrating	30(54.55%)
B2: Stricturing	15(27.27%)
B3: Penetrating	10(18.18%)
p: perianal disease	14(25.45%)

were represented by refractoriness to maximal medical therapy (6), malignancy (3), acute complications: toxic megacolon (6), perforation (1).

Crohn's disease group

Patients with Crohn's disease were classified according to the Montreal classification (see Table 6). Most patients (70.91%) had the age of onset between 17-40 years of age (A2), with the distal ileum as the most common location (38.18%) and with a more common non-structuring, non-penetrating pattern (54.55%). Perianal involvement was present in 25.45% of cases. The predominant clinical manifestations were: chronic watery diarrhea (61.82%), intestinal obstruction (12.72%), abdominal pain (9.09%), weight loss (7.27%), fever (5.45%).

When included in the study, 20.4% of patients were in clinical remission, while flare-ups were mild (25.9%), moderate (46.3%) and severe in only 7.4% of cases. Intestinal complications occurred in this group in a larger number (50.91%) than in the group with ulcerative colitis, the most common being stenosis (21.82%).

Extraintestinal manifestations were more frequent in this group compared to the group with ulcerative colitis (32.73%) - $p=0.001$; $OR=3.162$ (1.539-6.498). 16.4% had only one manifestation, 12.7% had two manifestations, and 3.6% had three extraintestinal manifestations. The most frequent were represented by arthritis (20%), ankylosing spondylitis (9.09%) and erythema nodosum (7.27%), as seen in Table 5.

Perianal disease group

Among patients with Crohn's disease, 14 (25.45%) presented perianal pathology. In this group, mean age at diagnosis was 30.29 ± 9.60 , these patients being 9.71 years younger than those without perianal pathology ($p=0.112$), with predominant female gender (64.29%). Perianal pathology was mostly associated with the complicated pattern of the disease - B2 and B3 (64.29%) and with location in the colon (57.14%). Indications for surgery reached a 57.14% percentage in this group.

Management of the CD

In this group, 8 patients (14.54%) required anti TNF alpha therapy and the indication for this type of therapy were lack of response to conventional treatment in 4 cases, perianal disease in 3 patients and 1 case with penetrating disease behavior. 21.81% from the CD patients were on azathioprine during the study period, while 30.9% required cortico-therapy - budesonide for small bowel involvement.

Surgery was required in a total of 21 patients (38.2%), 8 patients presenting with perianal pathology (drainage and fistulectomy, incision and perianal abscess drainage). Other indications for surgery in patients with Crohn's disease consisted of enteral and colonic stenosis, entero-enteral fistulas, and entero-vaginal fistulas.

Discussion

Ulcerative colitis and Crohn's disease represent two distinct forms of inflammatory bowel disease with unknown pathogenesis. Knowledge of incidence and prevalence rates in different geographical areas and different ethnic groups, as well as that of clinical and demographic characteristics of the population

studied may bring new information on the pathogenesis of these diseases (Ozin et al 2009). There is brief information in the literature about the epidemiology of inflammatory bowel diseases in Eastern Europe and very little about Romania, virtually the only prospective multicenter study in Romania dates from 2004 (Gheorghe et al 2004). This area was traditionally considered to be one of low incidence, but recent studies include Eastern Europe in the area with increasing incidence rates (Lakatos et al 2011, Burisch et al 2013). Therefore, our study brings some important demographic information.

In addition to the variation in the prevalence of IBD among different geographical areas, the ratio between UC and CD frequency also has some variations. If CD prevails in Western European countries and in America, there are some Eastern European countries, such as Croatia, where the ratio is 1:1 (Sincic et al 2006). A fact noted in developing countries but also for immigrants from these countries in developed countries is represented by the increase in the incidence of UC first, followed by the increase in the incidence of CD (Siew et al 2013). It is probably due to the changes in lifestyle, including diet, which may increase the risk of ulcerative colitis than that of Crohn's disease, requiring a greater number of years to modify the risk of developing Crohn's disease (Sunny et al 2013). In our study, UC/CD ratio is also 3/1.

Regarding our patients, mean age of onset in UC group is 40.18 years of age, similar to other Eastern European countries (Drapalo et al 2005). Crohn's disease patients are younger (mean age 36.98 years). Unlike Western countries, there is no bimodal distribution for age of onset in patients with inflammatory bowel disease, as it has also been described in other developing countries (Lovasz et al 2013).

Sex distribution of patients in our study is similar to that previously described in Western countries (Cosnes et al 2011, Burisch et al 2015), with a slight predominance of males in ulcerative colitis (male/female ratio = 1.17:1) and of females in Crohn's disease (male/female ratio = 1:1.75).

Our study reveals a very low incidence of positive family history, being present only in patients with UC (2.4%). This may reflect the increased incidence of IBD in this geographical area, in a population facing new environmental factors (Mak et al 2020, Langholz et al 2010). Patients in our study come from different ethnic groups (Romanian - the majority, Hungarian, Romani, Ukrainian). The small number of patients in each ethnic group does not enable the assessment of specific demographic characteristics and studies on a larger number of patients are required. The mean latency time between onset of symptoms and confirming diagnosis of IBD is longer in patients with CD (12.81 months) than in those with UC (4.25 months), probably due to the more non-specific symptoms of Crohn's disease. This value is higher than in Western countries probably due to lower accessibility to the means of diagnosis of patients, but also due to the low degree of suspicion for this pathology in a low incidence area. Flares of inflammatory bowel disease are common causes of absenteeism from work, similar to data from other Eastern European countries (Drapalo et al 2005).

Regarding smoking, literature reports show that non-smokers are more likely to develop ulcerative colitis and that smoking is a risk factor for the development of CD (Mahid et al 2006, Rogler et al 2016, Piovani et al 2019). In our study, more than

half of patients with UC never smoked, while 37.58% are former smokers. Moreover, in a small percentage of patients (3.03%), the causal relationship between quitting smoking and disease onset was quite clear (between 0.5 and 5.5 months).

There are several factors related to the methods of diagnosis used, performing total colonoscopy, defining disease extension, which make it difficult and less realistic to compare disease location in different studies. In our study, there are more patients with left-sided colitis among patients with ulcerative colitis (51.51%), similar to the literature data described for Western European countries, but also for countries in Asia (Wang *et al* 2007).

In patients with Crohn's disease, the most common site was the ileum (L1: 38.18%, L3: 30.915) and the most common pattern was the non-stricturing, non-penetrating pattern (B1), similar to Western European countries (Latella *et al* 2012). Practically, it is a population of patients in the early years of developing Crohn's disease (disease duration in these patients is $2.93 + 3.23$ years) which will probably develop a further complicated pattern. Perianal impairment was present in 25.45% of cases, most commonly in association with colonic involvement (57.14%). Data are similar to those previously described in Western countries (Ruffolo *et al* 2011).

The cumulative number of surgeries in CD appear to be similar to those described in previous studies in Eastern and Western European countries (Hovde *et al* 2012). Thus, 38.18% of CD patients underwent at least one surgery for complications due to illness or lack of response to treatment, compared to the group with UC where only 9.09% of patients underwent surgery ($p < 0.001$) before and during study. Among patients with CD surgery, 38.10% had undergone surgery for perianal pathology. Regarding disease location, L1 was most frequently associated with indications for surgery. These observations are similar to those described in Western European countries (Ramadas *et al* 2010). Thus, in the IBSEN study, the cumulative probability of surgery 10 years after diagnosis was 37.9% (Solberg *et al* 2007). Another study conducted in the United Kingdom reports a rate of surgery in the first 5 years after diagnosis ranging between 35 and 59%, depending on the time period studied (Lakatos *et al* 2011). As for UC, the rate described in our study is higher than in other Eastern European countries- 2.8% 5 years after diagnosis (Lakatos *et al* 2011), but comparable to some Western European countries (Hoie *et al* 2007). There is virtually no clear explanation for this, though there are differences between practitioners in terms of disease severity and indications for surgery. The frequency of extraintestinal manifestations in our study (13.33% in UC group, 32.73% in CD group, $p = 0.002$) is lower than that described in Western countries (43% in CD, 31% in UC) (Vavricka *et al* 2011). However, several studies report a higher frequency of extraintestinal manifestations in CD than in UC (Vavricka *et al* 2011, Stephan *et al* 2015). In our study, the most common manifestation in both types of inflammatory bowel disease was arthritis.

Conclusions

Nowadays, inflammatory bowel disease occurs more often in gastroenterological practice in Eastern European countries, including Romania. Epidemiological and clinical data are similar to those previously described in Western countries, with several particular therapeutic features probably related to the economic

background of these countries. Multicenter prospective studies are needed to emphasize several clinical and epidemiological features in each ethnic group.

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