Clinical Expression of Inflammatory Bowel Diseases – A Retrospective Population-Based Cohort Study; Vukovarsko-Srijemska County, Croatia, 2010

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A B S T R A C T

Clinical characteristics of the cohort of 150 patients with inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease (CD), Vukovarsko-Srijemska County, Croatia, were retrospectively assessed. UC was clinically presented with frequent passage of bloody, slimy stools, while preferential symptoms of CD were fever, anemia and severe weight loss, differences reflecting longer duration of symptoms prior to the diagnosis, in patients with CD. The prevalent disease localisations, in patients with UC, were the rectum and the left colon and the anorectum, while the prevailing phenotype, in patients with CD, corresponded with younger adult age at disease onset, ileocolonic localization and stricturing disease behavior. Intestinal complications, including perforation, fistula, abscess and ileus, were more prevalent in patients with CD. Of extraintestinal complications, only ankylosing spondylitis and erythema nodosum, reached marginally significant differences, in favor to patients with CD. Shortcomings of this study include the lack of associations and the time-dependent disease projections.

***Key words**: inflammatory bowel diseases, Crohn's disease, ulcerative colitis, symptoms, phenotypes, complications, a cross-sectional cohort study, North-Eastern Croatia*

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic intestinal conditions with common pathogenetic background and similar clinical expression, termed inflammatory bowel diseases (IBD)[1].

IBD mostly occur in adolescents and young adults and continue in a chronic manner. CD typically involves terminal ileum and the ascending colon, but can affect any part of the gastrointestinal tract, respecting a segmental, discontinuous form of spreading. In CD, inflammation may break throughout the wall, forming the granulomas, which later in the disease can be associated with the intestinal strictures and fistulas and the requirement for a surgical treatment[1,2]. UC involves the rectum and may spread to the colon, in an uninterrupted manner, sometimes affecting the entire colon. In UC, inflammation is localized in the mucosa and this is the reason why UC is not associated with the late surgical complications. However, in the case of severe bleeding, bloating, or a failure of the patient to respond to the medical treatment, surgery may be considered, by means of colectomy. Patients with UC are also at increased risk of colon cancer[3,4].

Both diseases are clinically presented with persistent diarrhea, hemorrhage and abdominal pain, and when the disease is severe, or of a long duration, also with weight loss, malnutrition and fever[1]. The symptoms tend to appear in flare-ups, with remissions in between. Due to

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chronic inflammation and the permanent activation of the immune system, in both diseases, a number of extra-intestinal complications can also appear, most of them being immunologically mediated, such as skin lesions, joint pain, eye inflammation and liver disorders[3].

According to these clinical characteristics, IBD is prominently a disabilitating disorder. Medical treatment is based on using drugs with antiinflammatory properties, including aminosalicylates, steroids, immune modifiers, antibiotics and biologic treatment (infliximab)[5]. Although there is evidence that these available therapeutic options have modified the natural history of IBD, they are not completely successful to provide the cure and relief from the long-lasting complications. There is an interest, therefore, within both, the research and the public communities, to gain insights into the causes of these diseases, to allow primary prevention and targeted therapy[5].

Many potential causing factors, for IBD, have been proposed to date[6,7]. Increasing evidence suggests IBD as complex, polygenic disorders with incomplete genetic penetrance and poor genotype-phenotype correlation[8]. Rapid changes in the epidemiologic pattern of these diseases, during the past decades, in Europe and wider in the world, provide the evidence that changes in lifestyles and environmental exposures are those dominant factors that drive clinical expression and the natural history of these diseases, while the genetic factors, although nowadays in the focus of research, have only permissive role[8,9]. There is an initiative, in the scientific community, to conduct long-term studies, in order to compare changes in environmental factors and treatment options with changes in the natural course and prognosis of IBD[4,5]. Standardization of the severity and the extension of a disease, necessary to making these comparisons, has recently been provided in the form of the Montreal's classification of IBD[10].

Aims

The second aim of the epidemiologic study, conducted in Vukovarsko-Srijemska County, continental Croatia, 2010 (see the paper entitled »Incidence and prevalence of inflammatory bowel disease in Vukovarsko-Srijemska County, Croatia, 1991–2000 and 2001–2010: a population-based study«), was to analyze clinical features of the cohort group of 150 patients with IBD, 119 with UC and 31 with CD, including information on: 1) symptoms and their duration at the first medical check up, taken separately for each of the two diagnoses, 2) the distribution of phenotypes, for both diseases, classified according to the Montreal's classification of IBD and 3) intestinal and extraintestinal complications.

Subjects and Methods

Data on subjects and methods are identical, as those ones already described in the paper entitled »Incidence and prevalence of inflammatory bowel disease in Vukovarsko-Srijemska County, Croatia, 1991–2000 and 2001–2010: a population-based study« (see page).

Statistical analysis

Descriptive statistics (expressed with absolute numbers of patients and percentages) were used to analyze the presence/absence of symptoms and complications, depending on the type of diagnosis. Differences among the categories were assessed by using the χ^2 and Fisher exact tests. The duration of the symptoms prior to the first medical check up (in months) was analyzed by using the nonparametric Mann-Whitney U-test. Distributions of phenotypes, particularly for UC and CD, were represented graphically, as columns of percentages. The extent of CD, according to the Montreal's classification (three stages per each of three categories: age at time of diagnosis, location and behavior, Table 7), was represented by using descriptive statistics (absolute numbers of patients and percentages), while differences among categories were analyzed by using χ^2-test.

In relation to UC, the Montreal's classification defines three phenotypes with respect to the extent of the disease and three severity stages (in addition to the stage »clinical remission«). In relation to CD, three categories of age at diagnosis, disease localization and behavior, are defined[10].

Results

Table 1 shows symptoms at the time of diagnosis and their distribution between two patient groups, one diagnosed with UC and the other diagnosed with CD. Significant difference was found in four symptoms, including: blood and slime in stool, stool frequency, fever and weight loss. Bloody and slimy stool was more typical for UC, with the number of stools per day exceeding four. Fever and severe weight loss (more than 10 kg), in the last three months, were more prominently present in patients with CD, although the latter symptom might be the result of the bias, due to the small number of patients in the group diagnosed with CD.

Duration of symptoms prior to the diagnosis was significantly longer in patients with CD (median around six months, with a quarter of patients having symptoms longer then a year) (Mann-Whitney U-test) (Figure 1). Median value for patients with the diagnosis of UC was around three months; a half of patients had symptoms duration between two and seven months (Figure 1).

Figure 2 shows distribution of phenotypes, in relation to the extent of the disease, in patients with UC, as defined according to the Montreal's classification. Although the results did not reach the significance level ($p=0.171$, χ^2-test), the phenotype presented with the maximum percentage of patients, 41.18%, was the phenotype E2 (left sided colitis, involving the colorectum). The phenotype E1 (proctitis), was at the second position, with 36.13%, and the phenotype E3 (extensive, pancolitis) – at the third position, with 22.69%.

In patients diagnosed with CD, the most frequent phenotype, according to the Montreal's classification, although the results were not statistically significant, was

TABLE 1
SYMPTOMS AT THE TIME OF DIAGNOSIS, FOR ULCERATIVE COLITIS AND CROHN'S DISEASE

Symptoms	Ulcerative colitis Number (%)	Crohn's disease Number (%)	p
Anemia			
Yes	55 (46.2)	22 (71.0)	0.014*
No	64 (53.8)	9 (29.0)	
Abdominal pain			
Yes	84 (70.6)	26 (83.9)	0.136*
No	35 (29.4)	5 (16.1)	
Bloody and slimy stool			
Yes	114 (95.8)	17 (54.8)	<0.001†
No	5 (4.2)	14 (45.2)	
The number of stools per day			
<1	0 (0)	2 (6.5)	
1–3	19 (16.0)	8 (25.8)	0.046†
4–7	52 (43.7)	11 (35.5)	
>8	48 (40.3)	10 (32.3)	
Fatigue			
Yes	76 (63.9)	23 (74.2)	0.280*
No	43 (36.1)	8 (25.8)	
Fever			
Yes	28 (23.5)	15 (48.4)	0.006*
No	91 (76.5)	16 (51.6)	
Joint pain			
Yes	36 (30.3)	11 (35.5)	0.576*
No	83 (69.7)	20 (64.5)	
Weight loss (kg) in the last three months			
Without loss	28 (23.5)	1 (3.2)	
1–2	12 (10.1)	3 (9.7)	
3–5	24 (20.2)	3 (9.7)	0.002*
6–9	25 (21.0)	5 (16.1)	
>10	30 (25.2)	19 (61.3)	
Total	119 (100)	31 (100)	

* – χ^2-test, † – Fisher's exact test

the phenotype A2L3B3 (younger adult age at disease onset, ileocolonic localization, penetrating behavior) (p= 0.117, χ^2-test) (Figure 3).

Distribution of the three defined categories, according to the age, localization and the disease behavior, showed a significantly higher proportion of patients with the ileocolonic localization of the disease (L3), without any preference under the categories age and behavior (p= 0.026, χ^2-test) (Table 2). However, the category 2 of age (age between 17 and 40 y at the onset of the disease) and the category 2 of behavior (stricturing) had a higher percentage of patients, in comparison to the rest two.

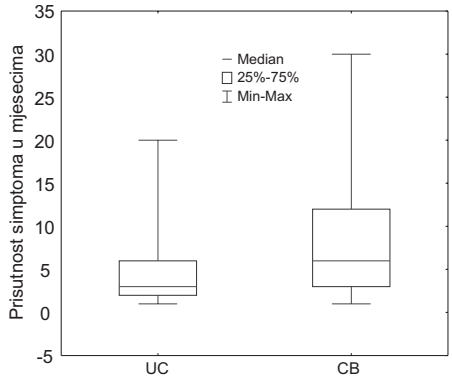

Fig. 1. Symptoms duration at the time of diagnosis (p=0.001; Mann-Whitneyjev U-test).

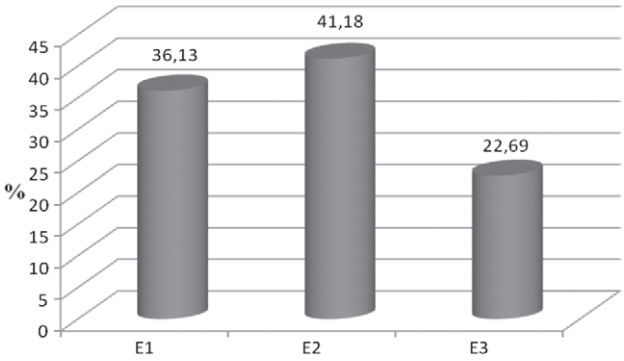

Fig. 2. Distribution of patients with ulcerative colitis (UC) according to the phenotypes (Montreal's classification).

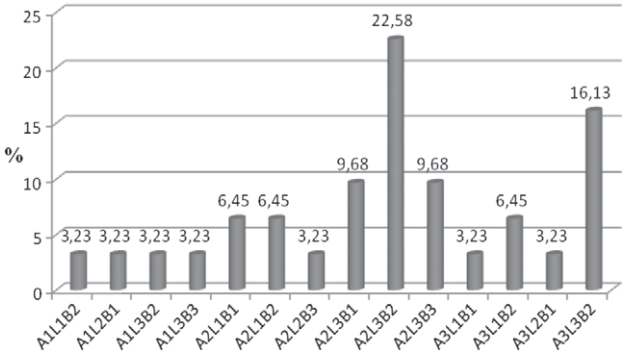

Fig. 3. Distribution of patients with Crohn's disease (CD) according to the phenotypes (Montreal's classification).

TABLE 2
THE EXTENT OF A DISEASE, FOR CROHN'S DISEASE, DEPENDING ON THE PHENOTYPES

Phenotype	1	2	3	p
A	4 (13)	18 (58)	9 (29)	0.087*
L	8 (26)	3 (10)	20 (64)	0.026*
B	8 (29)	18 (64)	5 (16)	0.125*

* – χ^2-test

Analysis of the intestinal complications, between two patient groups, showed significantly higher participation of complications in patients diagnosed with CD, then in those diagnosed with UC, including perforation, fistula, abscess and ileus (Table 3). There were no significant differences, between the groups, with respect to extraintestinal complications, except the tendency for the association between CD and Ankylosing spondylitis and Erythema nodosum (p=0.057 and 0.085, respectively, Fisher's exact test).

TABLE 3
INTESTINAL COMPLICATIONS, DISTRIBUTED BETWEEN THE PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

Symptoms	Ulcerative colitis Number (%)	Crohn's disease) Number (%)	p
Massive bleeding			
Yes	13 (10.9)	2 (6.5)	0.737*
No	106 (89.1)	29 (93.5)	
Toxic megacolon			
Yes	3 (2.5)	0 (0)	>0.950*
No	116 (97.5)	31 (100)	
Intestinal perforation			
Yes	1 (0.8)	3 (9.7)	0.028*
No	118 (99.2)	28 (90.3)	
Carcinoma			
Yes	0 (0)	1 (3.2)	0.207*
No	119 (100)	30 (96.8)	
Fistula			
Yes	1 (0.8)	7 (22.6)	<0.001*
No	118 (99.2)	24 (77.4)	
Abscess			
Yes	1 (0.8)	9 (29.0)	<0.001*
No	118 (99.2)	22 (71.0)	
Ileus			
Yes	1 (0.8)	8 (25.8)	<0.001*
No	118 (99.2)	23 (74.2)	
Total	119 (100)	31 (100)	

* – Fisher's exact test

When distributions of intestinal and extraintestinal complications were tested according to the sex (Males/Females), without preferences with respect to the specific diagnosis of IBD, significant results were obtained for the association between the female sex and massive rectal bleeding (Table 5) (p=0.044, χ^2-test).

TABLE 4
EXTRAINTESTINAL COMPLICATIONS, DISTRIBUTED BETWEEN THE PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

Complications	Ulcerative colitis Number (%)	Crohn's disease Number (%)	p
Acute arthritis			
Yes	24 (20.2)	8 (25.8)	0.495*
No	95 (79.8)	23 (74.2)	
Sacroiliitis			
Yes	3 (2.5)	3 (9.7)	0.103†
No	116 (97.5)	28 (90.3)	
Ankylosing spondylitis			
Yes	4 (3.4)	4 (12.9)	0.057†
No	115 (96.6)	27 (87.1)	
Erythema nodosum			
Yes	9 (7.6)	6 (19.4)	0.085†
No	110 (92.4)	25 (80.6)	
Pyoderma gangrenosum			
Yes	3 (2.5)	0 (0)	>0.950†
No	116 (97.5)	31 (100)	
Skin vasculitis			
Yes	0 (0)	1 (3.2)	0.207†
No	119 (100)	30 (96.8)	
Aphtous stomatitis			
Yes	29 (24.4)	9 (29.0)	0.595*
No	90 (75.6)	22 (71.0)	
Gallstones			
Yes	18 (15.1)	6 (19.4)	0.586†
No	101 (84.9)	25 (80.6)	
Renal stones			
Yes	15 (12.6)	2 (6.5)	0.526†
No	104 (87.4)	29 (93.5)	
Uveitis			
Yes	0 (0)	1 (3.2)	0.207†
No	119 (100)	30 (96.8)	
Episcleritis, conjunctivitis			
Yes	12 (10.1)	2 (6.5)	0.735†
No	107 (89.9)	29 (93.5)	
Liver fatty infiltration			
Yes	0 (0)	1 (3.2)	0.207†
No	119 (100)	30 (96.8)	
Primary sclerosing cholangitis			
Yes	1 (0.8)	1 (3.2)	0.372†
No	118 (99.2)	30 (96.8)	
Thromboembolic events			
Yes	1 (0.8)	0 (0)	>0.950†
No	118 (99.2)	31 (100)	
Amyloidosis			
Yes	0 (0)	0 (0)	>0.950†
No	119 (100)	31 (100)	
Total	119 (100)	31 (100)	

* – χ^2-test, † – Fisher's exact test

TABLE 5
INTESTINAL COMPLICATIONS, DISTRIBUTION ACCORDING TO THE SEX

Complications	Males Number (%)	Females Number (%)	p
Massive bleeding			
Yes	4 (5.2)	11 (15.1)	0.044*
No	73 (94.8)	62 (84.9)	
Toxic megacolon			
Yes	1 (1.3)	2 (2.7)	0.613†
No	76 (98.7)	71 (97.3)	
Intestinal perforation			
Yes	2 (2.6)	2 (2.7)	>0.950†
No	75 (97.4)	71 (97.3)	
Carcinoma			
Yes	1 (1.3)	0 (0)	>0.950†
No	76 (98.7)	73 (100)	
Fistula			
Yes	3 (3.9)	5 (6.8)	0.486†
No	74 (96.1)	68 (93.2)	
Abscess			
Yes	5 (6.5)	5 (6.8)	>0.950†
No	72 (93.5)	68 (93.2)	
Ileus			
Yes	6 (7.8)	3 (4.1)	0.496†
No	71 (92.2)	70 (95.9)	
Total	77 (100)	73 (100)	

* – χ^2-test, † – Fisher's exact test

Discussion

Discussion on symptoms at the time of diagnosis

Both IBD entities, UC and CD, in the early time--course of disease, may present with the same symptoms, including diarrhea and abdominal pain. Moreover, these symptoms may overlap with a functional intestinal disorder, called irritable bowel syndrome (IBS). This may be the reason of a delay in the exact diagnosis of IBD. The difficulties with at time diagnosis of IBD are also associated with the need for the invasive technique, colonoscopy, presently available to making the initial diagnosis. The question, a clinician is faced with, is when is it the right time to recommend colonoscopy[11]. Early diagnosis confirmation is, however, essential for effective treatments, especially important in the case of CD, where the severity of disease and a predisposition for penetrating/stricturing disorders is a function of disease duration[5,12].

According to our results, there was a significant difference between patients with UC and CD, in prevalence of symptoms at the time of diagnosis. Bloody and slimy stools, with frequent loose stool (>4 per day), was a typical clinical presentation of patients with UC ($p<0.001$ and $p=0.046$, respectively, Fisheržs exact test) (Table 1). Fever, anemia and severe weight loss (more then 10 kg in the past three months), were more prominent symptoms in patients with CD (Table 1). Fever was not specific enough for CD, as there was the equivalent percentage of patients with this diagnosis not having fever (Table 1).

These differences in clinical presentation of two diseases might be reflective of a significant difference in symptoms duration prior to the diagnosis (Figure 1). In this regard, due to localization of the pathologic process in the ileum, clinical presentation of CD may not be so expressive, as it is in the case of UC, where inflammation affects the outgoing part of the gastrointestinal tract, that is, the colorectum. More clear symptoms, suspected on CD, do not appear unless CD is in advanced stage of the pathologic process, presenting, e.g. (as our results also show), with anemia and weight loss (Table 1)[11]. In this sense, our results also indicate a longer symptoms duration prior to the diagnosis in patients with CD (median 6 months), then in patients with UC (median 3 months) (Figure 1). Moreover, even a quarter of patients with CD have been conscious of the symptoms over a year before the diagnosis (Figure 1). For clinicians, it could be of importance to develop an early, non-invasive risk prediction tool, to search for high risk patients for IBD and, in particular, for CD, who might be candidates for the invasive diagnostics. Some efforts have already been taken, by adding new biologic and genetic markers, to the clinical manifestations of IBD[13].

Another potential reason of these differences in symptoms between two patient groups in our sample, might be a higher proportion of males, among patients with CD (M/F, 64.5%/35.5%), that is opposite to what is generally cited in the literature[1]. We can speculate that younger men may contact doctor later in the course of the disease, as being less sensitive, then females, on insufficiently defined sensations coming from their stomach. Or, there can be a difference in clinical presentation of CD, or IBD in general, between men and women. In favor to the latter presumption, our results on intestinal complications indicated that one symptom, massive rectal bleeding, had the sex preference, showing an association with the female sex (Table 5). In contrast, the literature citations indicate that the problem of a delay in diagnosis of IBD, and especially of CD, is present elsewhere; so, the issue of an early diagnosis of IBD remains as a challenge for the future[11].

Discussion on phenotypes

The recent clinical classification of IBD, including both, UC and CD, has been provided by the Montrealžs classification[10]. The clinical usefulness includes the possibility to assess the prognosis and to choose more appropriate therapeutic options. The benefit provided to the basic science includes better understanding the pathophysiology of the different clinical manifestations of IBD. The progress in knowledge on serologic and genetic mar-

kers, has also been considered, with the potential to subclassify disease and to make projections for further research[8,10].

With respect to the extent of UC, our results indicate that the most prominent phenotype, in our sample, is localization of disease in the rectum and the left colon (phenotype E2, according to the Montrealžs classification), with 41% of patients, then follows the phenotype E1 (proctitis), with 36% of patients, and at the third position is the extensive type of disease (proximal to the splenic flexure), including also pancolitis (phenotype E3), with 23% of patients (Figure 2). Since this distribution has not reached the statistically significant level, the results cannot be strictly compared with the results obtained in other cohort populations[14]. For example, in the prospective Norwegian study, patients were equally distributed, that means, one third of patients per each localisation[15]. To make a fairly good comparison between different studies, with respect to the extent of disease, information on disease duration will also be needed, as the proximal extent of inflammation has a tendency to progress over time[12]. Data collected in previous studies suggest an increase over 50% in cumulative prevalence of patients with pancolitis, after 20 years of disease duration[16].

According to the Montrealžs classification, in addition to data on the extent of disease, information on severity of symptoms and disease activity, at the time of diagnosis, are also important (see the Methods), to serve as predictors of colectomy, or as the basis to planning immunomodulating, or biologic therapy, if disease is properly severe[10]. In this context, analysis of symptoms, in this study, showed that a passage of more than four bloody, slimy stools per day, is the best way to describe the clinical characteristics of the patients in the sample, corresponding with the severity stage S2 (moderate) (see the Methods). However, much of our knowledge does not yet provide clear-cut answers; so this is the severity of the initial disease which cannot indicate prognosis, because the disease activity tends to decrease over time[17,18].

When analysis of phenotypes of CD was made, the results showed the class age 17–40 y as the prevalent age at disease onset (phenotype A2, according to the Montreal's classification), with 58% of patients, the ileocolon as the predominant disease localization (phenotype L3), with 64% of patients, and stricturing complication as the dominant disease behavior (phenotype B3), with 64% of patients (Table 2). Altogether, from these results, the most prevalent integrated phenotype in the sample, A2L3B3, has arisen, presented with 22.58% of patients (Figure 3). Systematic review data also indicate the prevalent participation of the ileocolonic disease at the time of diagnosis, compared to isolated small bowel disease and pure colonic disease[12,19].

The results of the previous studies have taught us that the localization of CD maintains relatively stable over the course of the disease. In contrast, the disease behavior is more susceptible to changes with increasing disease duration[12,20]. For this reason, prospective studies,

TABLE 6
EXTRAINTESTINAL COMPLICATIONS, DISTRIBUTION ACCORDING TO THE SEX

Complications	Males Number (%)	Females Number (%)	p
Acute arthritis			
Yes	13 (16.9)	19 (26.0)	0.172*
No	64 (83.1)	54 (74.0)	
Sacroiliitis			
Yes	4 (5.2)	2 (2.7)	0.682†
No	73 (94.8)	71 (97.3)	
Ankylosing spondylitis			
Yes	5 (6.5)	3 (4.1)	0.720†
No	72 (93.5)	70 (95.9)	
Erithema nodosum			
Yes	7 (9.1)	8 (11.0)	0.703*
No	70 (90.9)	65 (89.0)	
Pyoderma gangrenosum			
Yes	2 (2.6)	1 (1.4)	>0.950†
No	75 (97.4)	72 (98.6)	
Skin vasculitis			
Yes	0 (0)	1 (1.4)	0.487†
No	77 (100)	72 (98.6)	
Aphtous stomatitis			
Yes	18 (23.4)	20 (27.4)	0.571*
No	59 (76.6)	53 (72.6)	
Gallstones			
Yes	8 (10,4)	16 (21.9)	0.054*
No	69 (89.6)	57 (78.1)	
Renal stones			
Yes	12 (15.6)	5 (6.8)	0.092*
No	65 (84.4)	68 (93.2)	
Uveitis			
Yes	0 (0)	1 (1.4)	0.487†
No	77 (100)	72 (98.6)	
Episcleritis, conjunctivitis			
Yes	9 (11.7)	5 (6.8)	0.309*
No	68 (88.3)	68 (93.2)	
Liver fatty infiltration			
Yes	1 (1.3)	0 (0)	>0.950†
No	76 (98.7)	73 (100)	
Primary sclerosing cholangitis			
Yes	2 (2.6)	0 (0)	0.497†
No	75 (97.4)	73 (96.8)	
Thromboembolic events			
Yes	0 (0)	1 (1.4)	0.487†
No	77 (100)	72 (98.6)	
Amyloidosis			
Yes	0 (0)	0 (0)	>0.950†
No	77 (100)	73 (100)	
Total	77 (100)	73 (100)	

* – χ^2-test, † – Fisher's exact test

TABLE 7
THE MONTREAL'S CLASSIFICATION OF INFLAMMATORY BOWEL DISEASE MONTREAL CLASSIFICATION OF THE EXTENT OF ULCERATIVE COLITIS

Extent	Anatomy
E1 (Ulcerative proctitis)	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2 (Left sided UC – distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3 (Extensive UC – pancolitis)	Involvement extends proximal to the splenic flexure
Montreal classification of severity of ulcerative colitis	
Severity	Definition
S0 – Clinical remission	Asymptomatic
S1 – Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (Erythrocyte Sedimentation Rate)
S2 – Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3 – Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5 °C, Haemoglobin of less than 10.5 g/100 mL, and Erythrocyte Sedimentation Rate of at least 30 mm/h
Montreal classsification for Crohn's disease	
Age at diagnosis	A1 – below 16 y
	A2 – between 17 and 40 y
	A3 – above 40 y
Location	L1 – ileal
	L2 – colonic
	L3 – ileocolonic
	L4 – isolated upper disease (a modifier that can be added to L1-L3 when concomitant upper disease is present)
Behaviour	B1 – non-stricturing, non-penetrating
	B2 – stricturing
	B3 – penetrating
	P – perineal disease modifier (is added to B1-B3 when concomitant perineal disease is present)

with a long time of follow-up, have advantages over the cross-sectional and retrospective ones[4,14]. Results of the early studies indicated three types of CD behaviors, including penetrating, stricturing and nonpenetrating/nonstricturing (inflammatory), in addition to perianal disease[10]. At the time of diagnosis, the inflammatory form predominates (corresponding with symptoms such as fever, anemia and weight loss) and the risk of complications (development of strictures or fistulas) increases with the time of follow-up[12,20]. In the Olmsted County population, Minnesota, USA, the 20-year cumulative rate of all complications counted more than 60%[21]. According to the Norwegian prospective study, 53% of patients developed stricturing or penetrating disease at 10 years of follow-up[15].

Also important, from the prognostic perspective, is the fact that disease localization influences its evolution, with ileal disease being more often stricturing and colonic and ileocolonic disease – more often penetrating. In addition, colonic disease remains uncomplicated for many years, while small bowel disease may be complicated early after the diagnosis[22,23]. More recent studies indicate also the role of the genetic risk factors on the prognosis of CD and IBD and the potential influence of early introduction of immunomodulatory or biologic therapy, in slowing down disease progression and altering the natural history of IBD[13,24,25].

Discussion on complications

As already mentioned, it is well known that patients with CD are more prone to develop late intestinal complications, either as stricturing, or penetrating, or as their combinations. This is why the majority of patients with CD need surgery within 10 years of diagnosis[14,26]. Predisposition to these complications is due to deep inflammation, tending to affect the whole wall thickness. Strictures and luminal opstructions (clinical correlates of ileus) may be either on the basis of inflammatory mass (including abscess formation), or fibrotic tissue formation. In fact, stricture and fistula are often found in proximity of one another, as fistula develops to decompress the lumen at the site of stricture[27]. Our results are in line with these pathologic features, indicating significantly higher participation of intestinal complications, in patients with CD, than in those with UC. These registered complications include: intestinal perforation (CD/UC,

9.7%/0.8%), fistula (CD/UC, 22.6%/0.8%), abscess (CD/UC, 29.0%/0.8%) and ileus (CD/UC, 25.8%/0.8%) (Table 3). Although these results do not indicate the proportion of patients who needed the surgical intervention, data yet allow some comparisons. For example, studies from Olmsted County, Minnesota, USA, reported that 41% of patients with CD underwent at least one resection, and 57% of patients – at least one operative procedure[28,29].

It is well known that extraintestinal manifestations are common in both UC and CD[3,30]. Some of these manifestations can be prescribed to nutritional and metabolic disturbances, secondary to chronic intestinal inflammatory process, such as, e.g., gallstones, or renal stones, osteoporotic, fatty liver, or thromboembolic disorders[3,31,32]. In considering causes, of note is also the impact of corticosteroid therapy. As causes of other extraintestinal manifestations, including primary sclerosing cholangitis, ankylosing spondylitis, iritis/uveitis, pyoderma gangrenosum, erythema nodosum and demyelinating disorder – cross-reacting autoantibodies have been proposed[33]. According to the results of the Manitoba study (Canada), as much as 6.2% of patients with IBD developed some of these manifestations, 10 years or more after the diagnosis[34]. In the IBSEN cohort study, the overall prevalence of spondyloarthropathies, in patients with CD, was 26%, while 6% of patients had ankylosing spondylitis (73% HLA-B27 positive)[35]. In our sample, patients with CD had higher (although of a marginal significance) proportion of cases with immunologicaly mediated extraintestinal disorders, ankylosing spondylitis and erythema nodosum, than patients with UC. This seems logical, as CD, in contrast to UC, is considered as autoimmune disorder[36]. Relatively high percentage of patients with ankylosing spondylitis (12.9%) may be the artefat of the small sample, or of imprecise diagnosis, as cases with non-specific spondyloarthropathies might have also been taken into account.

Conclusions / Limitations

This analysis of the clinical characteristics of the cohort population, diagnosed with IBD, was performed as the part of the epidemiologic study, aimed at assessing the incidence and prevalence of UC and CD, in Vukovarsko-Srijemska County, Croatia. Patients were interviewed retrospectively, by using standardised protocols, on age and symptoms at the time of diagnosis, intestinal and extraintestinal complications and the localization and the extent of disease. Based on these latter peaces of information, phenotypes, defined by using the Montralžs classification, were determined accordingly. Since data are used in a cross-sectional and retrospective manner, many important, timely-based associations are missing. Based on this analysis, it is not possible, for example, to determine types of complications in relation to disease duration, or the time-dependent and the treatment-dependent evolution of disease. Conclusions on the impact of changes in environmental risk factors and demographic features, on the natural course and spreading of IBD, are also not possible to make. However, this study might be the starting position in developing the national register of patients with IBD, necessary if someone wants to continuously follow-up changes in frequency and characteristics of IBD. Only such, dynamical approach, will allow causal relationships, essential for the purpose of designing advanced therapeutic options.

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KLINIČKE ZNAČAJKE KRONIČNIH UPALNIH BOLESTI CRIJEVA – RETROSPEKTIVNA POPULACIJSKA KOHORTNA STUDIJA VUKOVARSKO-SRIJEMSKE ŽUPANIJE, HRVATSKA, 2010.

S A Ž E T A K

Kliničke značajke kohortne skupine od 150 pacijenata, s upalnim bolestima crijeva, uključujući ulcerozni kolitis (UC) i Cronovu bolest (CB), iz Vukovarsko-srijemske županije, Hrvatska, su retrospektivno ispitivane. Najvažnije kliničke značajke pacijenata s ulceroznim kolitisom su bile učestale krvave i sluzave stolice, a u pacijenata s CB, to su bili vrućica, anemija i jači gubitak tjelesne mase, što je dijelom odraz i dužeg trajanja simptoma prije vremena dijagnoze, u pacijenata s CB. Vodeće lokalizacije bolesti, u pacijenata s UC, su bile rektum i lijevi kolon te anorektum, dok je najzastupljeniji fenotip, u pacijenata s CB, odgovarao mlađoj, odrasloj dobi pri postavljanju dijagnoze, lokalizaciji bolesti u ileokolonu, te tipu bolesti karakteriziranoj sklonošću ka razvoju crijevnih striktura. Intestinalne komplikacije, perforacija, fistula, absces i ileus, su bile učestalije u pacijenata s CB. Od ekstraintestinalnih komplikacija, samo su ankilozirajući spondilitis i nodozni eritem i to samo granično značajno više bili zastupljeni u pacijenata s CB. Glavni nedostatak ove studije je izostanak ispitivanja povezanosti te vremenski-ovisne projekcije bolesti.