Epidemiology and Clinical Presentation of Inflammatory Bowel Disease in Zadar County, Croatia

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ABSTRACT

Results of the retrospective, population-based study, 2000–2010, on inflammatory bowel disease, ulceratice colitis (UC) and Crohn's disease (CD), from Zadar County, have been presented and compared with world experience and comparative data from Primorsko-Goranska and Vukovarsko-Srijemska Counties. The average incidence rates (per 100 000) were 8.2 and 8.4, for UC and CD, respectively. Prevalence rates, at the end of the follow up, were 133.9 for UC and 111 for CD. Constant increase in the incidence rates for both, UC and CD, have been recorded, for CD more prominently in the second part of the follow up, 2006–2010. Prevalence rates have being continuosly rased for both diseases, data for UC exceeding that for CD. Results of data comparison among the counties contribute in favour to the hypothesis of Zadar County as a rapidly developing area and strongly argue against the existence of the North-South gradient between Vukovarsko-Srijemska and Zadar Counties.

***Key words**: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, retrospective population-based study, Zadar County, Croatia*

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are two similar chronic inflammatory disorders of the intestine, typically presented with the exchange of exarcebations and remissions[1]. Exacerbation symptoms include abdominal pain, diarrhoea, gastrointestinal bleeding, raised body temperature, fatigue and weight loss. Long disease duration is also associated with malnutrition and the development of chronic intestinal and extraintestinal complications[2]. In the case of CD, chronic intestinal complications usually require surgical interventions[3]. Extraintestinal complications are the result of chronic inflammation associated with metabolic disturbances and immune activation and can be presented with a variety of manifestations, including skin, joint, eye and the hepatobiliary system disorders[4]. Due to many symptoms and the chronic course characterized with the development of complications, IBD have also a substantial impact on the quality of life and difficulties of living with chronic disease issues[5].

Although both diseases share many clinical and pathogenetic features, they yet show differences, sufficiently enough to acquire characteristics as two separate disorders. In CD, pathologic changes usually involves terminal ileum and the ascending colon, but can affect any part of the gastrointestinal system, from the mouth to the anus. Inflammatory process is associated with lymphocyte infiltration and granulomas formation and encompasses the whole wall thickness, with spreading also to the mesenterial lymph nodes, mesenterium and the peritoneal cavity. It is characterized with deep ulcers and fissures, which are later substituted with progressive fi-

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brosis and the formation of stenosis and fistulas. In UC, the inflammatory process maintains localised in the mucosa and is mediated mainly by neutrophil granulocytes infiltration. It is characterized with the crypt abscess formation and the hypertrophy of the rest of the mucosa, the state known as pseudopolyposis, which later during the course of the disease reverts to the mucosal atrophy and the intestinal retraction. Pathologic process typically involves the rectum and may spread continuously to the colon, sometimes affecting the entire colon[2,4].

In spite of much progress made in understanding the pathophysiology of IBD, it is still largely unknown. Recent findings suggest the disruption of the gut immune homeostasis and the epithelial cells regulatory mechanisms, which then lead to the abnormal immune responses to commensal bacteria and chronic intestinal inflammation[6]. Although certain IBD susceptibility genes have been identified so far, it does not contribute much to planning prevention, as evidence suggest that changes in lifestyles and environmental exposures are those factors that drive the spread and clinical expression of these diseases, while genetic factors have only the permissive role[7,8]. In line to this, recent epidemiologic studies indicate rapid changes in the epidemiologic patterns of IBD in the last two decades. Traditionally, the highest incidence and prevalence of UC and CD have been reported in the developed areas of Northen Europe and North America, with the gradient observed to exist from North to South and, to a lesser degree, from West to East[1,9]. Some theories have been coined to explain observed differences in the spread of IBD. An explanation provided to support the North to South gradient includes differences in climate and the number of sunny days per year, between the northern and the southern countries[9]. The Hygiene hypothesis has been used to explain the West to East gradient. It indicates that the high sanitation level, wide antibiotics use and mandatory vaccination are these factors which, in the developed Westernian countries, cause poor immunization of children to microbial antigens and the breakdown of the immunologic tolerance later in life, leading to the development of IBD[10]. In contrast to the traditional epidemiologic situation, IBD has now being emerged in regions where they have rarely been, or have not been at all registered before, such as countries of Eastern Europe, continental and South-East Asia and North Africa[11–14]. In developed countries, stagnation, or a slowdown, has been recorded[1]. It has been generally accepted that these recent epidemiologic features indicate emergency of IBD as a global disease, which is likely to correspond with the westernised lifestyles, including factors such as smoking, diets high in fat and sugar, widespread use of medications and psycho-social stress[15].

The epidemiologic studies on IBD in Croatia have already been performed in Primorsko-Goranska (P-G) and Vukovarsko-Srijemska (V-S) Counties (Figure 1). In this

Fig. 1. Division of Croatia on counties. Counties of the interest for this paper: Zadar County, Primorsko-Goranska and Vukovarsko-Srijemska Counties.

paper, the results for Zadar County have been presented and compared with these previous results, as well as with world knowledge.

Subjects and Methods

Subjects

Patients diagnosed with IBD (UC or CD) and living in Zadar County were included in the study. According to the last census, 2001, there were 162 045 citizens in Zadar County, distributed on the surface area of 3646 km^2, which makes density of 44.4 citizens per 1 km^2. The prevalent contribution was from the urban area (61.7%).

The total number of eligible patients was 397. Of them, 217 were diagnosed with UC (54.6%) and 180 with CD (45.4%). There were 243 (61.2%) males and 154 (38.8%) females. The inclusion criteria were defined as the combination of clinical symptoms and signs and endoscopic, radiology and hystopathology reports. Patients with nonclassified IBD and those with coprocultures positive on bacterial causes of diarrhoea, or those previously receiving antibiotics, were excluded from the analysis.

Methods

The same design as in the recently reported study from V-S County has been applied. For the beginning, the patient list was formed, using documentation of the General Hospital Zadar and two private enterprises. The 10-year period, 2000–2010, was used. Prevalence data were estimated according to the number of patients diagnosed with IBD until January 1st 2010, inclusive. Patients were contacted personally, or by phone, and interviewed according to two types of questionnaires, adapted to data collection on either the incidence or prevalence of IBD.

Protocols were identical in parts addressing issues such as: patients general data, demographic features, education, employment status, family history of IBD and risk factors. Some parts of both questionnaires were devoted specifically to disease data, including information on: the type and time of the diagnosis, symptoms and their duration prior to the first medical check up, body weight at the time of the first physical examination, weight loss in the last three months, performed diagnostic procedures and the extent of a disease. The protocol adapted to data collection on prevalence of IBD was extended for the part addressing issues, such as: the natural history of a disease, the presence/absence of the intestinal and extraintestinal complications, the number and types of surgical interventions and the results of pathohistological examinations. According to these latter data, phenotypes of both, UC and CD, were determined, by using the Montreal classification[16].

Statistics

Statistical analyses were performed by using statistical software package SPPS 10.0 (SPSS for Windows, SPSS Inc. Chicago IL, USA). Categorical data were presented as absolute frequences and percentages. Differences between groups were assessed by using the student's t-test for two independend samples. Absolute frequences were assessed by using χ^2-test and, where appropriate, Fisher exact test. The level of significance of $p<0.05$ was considered statistically significant.

Results

Demographic data analysis

Comparative analysis of demographic features between the two patient groups showed that males were prevalent in both patient groups and that there were no differences in males to females proportions, depending on the type of diagnosis (Table 1). Differences between patients with UC and CD were found in: 1) marital status (higher percentage of married persons among those diagnosed with UC), 2) level of education (the prevailing proportion of those with secondary school against those with lower level education, among patients with CD), 3) the status of employment (unemployed persons were more frequently presented among patients with CD, while

TABLE 1.
DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH UC AND CD WITH χ^2 TEST RESULTS

	UC – Number (%)	CB – Number (%)	p*
Distribution of subjects by gender			
M	128 (59)	115 (63.9)	0.319
F	89 (41)	65 (36.1)	
Distribution of subjects by marital status			
Married	181 (83.4)	106 (58.9)	<0.05
Unmarried	29 (13.4)	72 (40.0)	
Divorced	2 (0.9)	1 (0.6)	
Widow(er)	5 (2.3)	1 (0.6)	
Distribution of subjects by resident status			
Immigrant to Zadar County	35 (16.1)	15 (8.3)	<0.05
Born in Zadar County	182 (83.9)	165 (91.7)	
Distribution of subjects by the level of education			
Primary school	10 (4.6)	2 (1.1)	<0.05
Vocational school	6 (2.8)	5 (2.8)	
Secondary school	148 (68.2)	144 (80.0)	
University education	53 (24.4)	29 (16.1)	
Distribution of subjects by the employment status			
Employed	126 (58.1)	110 (61.1)	<0.05
Unemployed	23 (10.6)	34 (18.9)	
Retired	48 (22.1)	18 (10.0)	
Housekeepers	12 (5.5)	4 (2.2)	
Students	8 (3.7)	14 (7.8)	

* χ^2-test

those retired were more frequently presented in the group of patients with UC) and 4) the resident status (higher percentage of immigrants among patients with UC) (Table 1). In addition, patients with CD were, in average, younger then those with UC (31.9 and 42.2 years, respectively) (Figure 2).

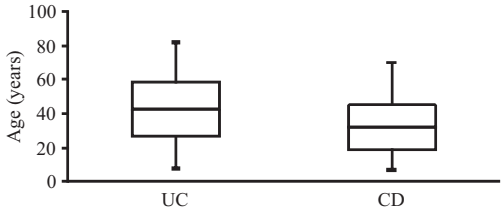

Fig. 2. Distribution of patients with UC and CD by age (t-test p<0.001).

The average incidence rates for UC and CD, in Zadar County, for the 10-year period of observation, 2000–2010, were 8.2 and 8.4 per 100 000, respectively. Prevalence rates, estimated at the end of the follow up, were 133.9/100 000 for UC and 111/100 000 for CD. An increase in the incidence rates for both, UC and CD, have been recorded, more prominently visible for CD in the second part of the follow up, 2006–2010 (Figure 3).

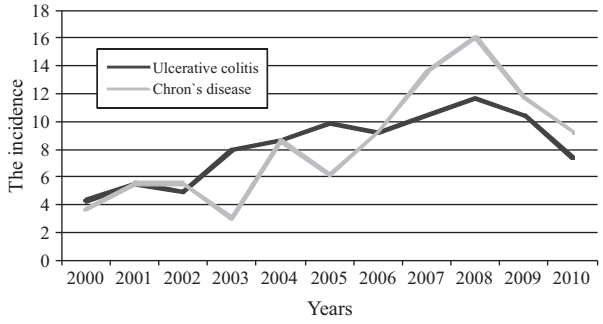

Fig. 3. The incidence rates for UC and CD across the years 2000–2010.

In the period of observation, prevalence rates have being continuosly rased for both diseases, data for UC exceeding that for CD (Figure 4). Two time points of acceleration in prevalence rates uprise can be observed, including years 2004 and 2006 (Figure 4).

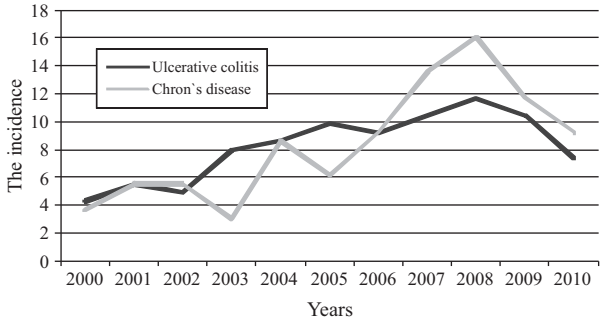

Fig. 4. Prevalence rates for UC and CD across the years 2000–2010.

The incidence and prevalence data for Zadar County were compared with the corresponding data for two other counties, P-G and V-S, where the epidemiologic studies have already been performed. However, this comparison was restricted to the period of the data overlap, that is, for the years 2000–2004 (Tables 2–4). Based on these comparisons, it is visible that the average incidence rate for UC is higher in Zadar County than in P-G County (6.2 against 4.6) (Table 2), while the highest average incidence rate for CD is in P-G County (6.5), overcoming that in Zadar County (5.2) (Table 3). Prevalence rates for both diseases, UC and CD, are the highest in P-G County, the difference particularly prominent for CD, compared to Zadar County (Table 4). In comparison to these two counties, in V-S County, much lower corresponding values for the average incidence and prevalence rates have been recorded, especially for CD (Table 2–4).

TABLE 2.
THE INCIDENCE RATES FOR UC FOR THE PERIOD 2000–2004, COMPARISON BETWEEN THREE COUNTIES

	Zadar County	Vukovarsko-srijemska County	Primorsko-goranska County
2000	4.3	1.0	6.9
2001	5.5	2.0	5.6
2002	4.9	1.0	3.9
2003	8.0	2.0	3.3
2004	8.6	2.0	3.3
Average	6.2	1.6	4.6

TABLE 3.
THE INCIDENCE RATES FOR CD FOR THE PERIOD 2000–2004, COMPARISON BETWEEN THREE COUNTIES

	Zadar County	Vukovarsko-srijemska County	Primorsko-goranska County
2000	3.7	0.5	7.9
2001	5.5	0.0	5.9
2002	5.5	1.0	5.9
2003	3.0	0.0	5.9
2004	8.6	1.0	7.2
Average	5.2	0.5	6.5

TABLE 4.
PREVALENCE RATES FOR UC AND CD FOR THE YEAR 2004, COMPARISON BETWEEN THREE COUNTIES

Year 2004	Zadar County	Vukovarsko-srijemska County	Primorsko-goranska County
Ulcerative colitis	74.7	19.0	84.9
Crohn's disease	45.0	6.3	83.7

Analysis of symptoms, signs and phenotypes

Analysis of symptoms and signs at the time of diagnosis showed certain differences in clinical presentation of UC and CD (Table 5). Also, a statistically significant difference was found in the average duration of symptoms, prior to the diagnosis. In patients with UC, it lasted in average 3.5 months and in patients with CD 6.6 months (Figure 5).

The most common clinical presentation of patients with UC included moderately frequent (4–7 times per day) bloody and slimy stools. In the case of CD, it was abdominal pain and more general symptoms, including fatigue, fever and weight loss (Table 5).

Analysis of phenotypes, based on using the Montreal's classification, indicated the extent of either of a disease. Patients with UC were most commonly presented with the phenotype E3 (indicating extensive colitis, or pancolitis). However, the difference did not reach the significance level, not either in relation to two other phenotypes (E1 – proctitis and E2 – the colorectum and the left side of the colon) (χ^2-test, p=0.81), nor in relation to males/females distribution (χ^2-test, p=0.21) (Figure 6).

TABLE 5.
SYMPTOMS AND SIGNS AT THE TIME OF DIAGNOSIS FOR ULCERATIVE COLITIS AND CROHN'S DISEASE

Symptoms	Ulcerative colitis Number (%)	Crohn's disease Number (%)	p
Anemia			
Yes	83 (38.2)	71 (39.4)	p >0.05*
No	134 (61.8)	109 (60.6)	
Abdominal pain			
Yes	134 (61.8)	135 (75.0)	p<0.05*
No	83 (38.2)	45 (25.0)	
Bloody and slimy stool			
Yes	205 (94.5)	51 (28.3)	p<0.05†
No	12 (5.5)	129 (71.7)	
The number of stools per day			
1–3	50 (23.0)	81 (45.0)	p<0.05†
4–7	151 (69.6)	91 (50.6)	
>8	16 (7.4)	8 (4.4)	
Fatigue			
Yes	107 (49.3)	120 (66.7)	p<0.280*
No	110 (50.7)	60 (33.3)	
Fever			
Yes	49 (22.6)	86 (47.8)	p<0.006*
No	168 (77.4)	94 (52.2)	
Weight loss (kg) in the last three months			
Yes	87 (40.1)	112 (62.2)	p<0.05*
No	130 (59.9)	68 (37.8)	

* χ^2-test, † Fisher's exact test

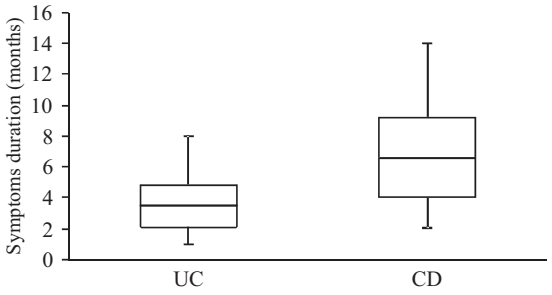

Fig. 5. Duration of symptoms prior to the diagnosis for ulcerative colitis and Crohn's disease (t-test; p<0,001).

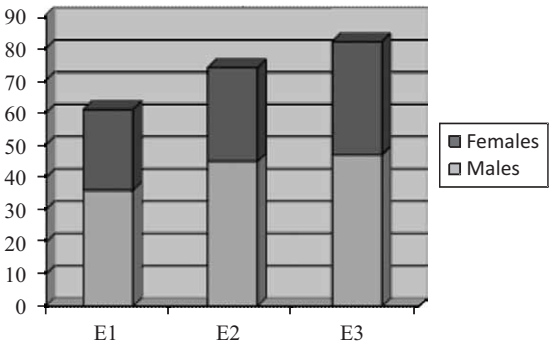

Fig. 6. The distribution of phenotypes, identified according to the Montreal's classification, in patients with UC.

The most common phenotypes, in patients with CD, based on using the Montreal's classification, were A2L1B1 (20.8%), A2L3B1 (13.9%) and A2L2B1 (8.1%), where A indicates age, L – localisation and B – disease behaviour (Figure 7). By considering particular respective parameters, then significantly higher percentage of patients were in the age group A2 (17–40 years) (62.8%) and had disease localisation in the terminal ileum (L1) (41.6%), or in the terminal ileum and the colon (L3) (35.6%), or in the colon alone (L2) (22.8%). With respect to disease behaviour, the significantly highest percentage of patients (72.8%) had the phenotype B1 (noncomplicated disease) (Table 6).

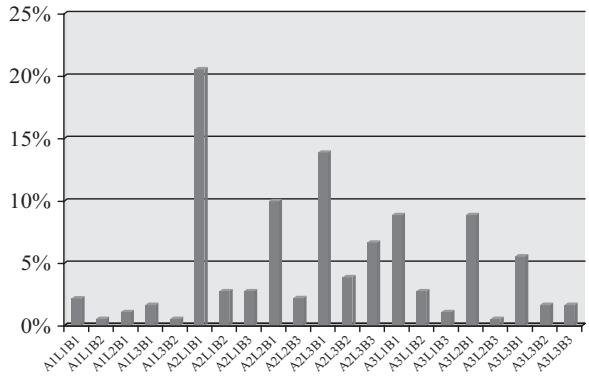

Fig. 7. The distribution of phenotypes, identified according to the Montreal's classification, in patients with CD.

TABLE 6.
PHENOTYPES, IN PATIENTS WITH CD, ACCORDING TO THE PARTICULAR RESPECTIVE PARAMETERS, INCLUDING AGE (A), LOCALISATION (L) AND DISEASE BEHAVIOUR (B)

Fenotype	1	2	3	p*
A	11 (6.1%)	113 (62.8%)	56 (31.1%)	p<0.01*
L	75 (41.6%)	41 (22.8%)	64 (35.6%)	p<0.01*
B	131 (72.8%)	22 (12.2%)	27 (15.0%)	p<0.01*

* χ^2-test

Analysis of intestinal and extraintestinal complications

Analysis of intestinal complications, between the two patient groups, showed significantly higher participation of complications that require surgical treatment in patients with CD, including perforation, fistula, abscess and ileus. The percentage of patients already experienced some surgical treatments was also higher among those diagnosed with CD (Table 7). Intestinal complications, found to be more frequently presented in patients with UC, included massive rectal bleeding, toxic megacolon and colorectal cancer (Table 7).

With respect to extraintestinal complications, the results of comparison between the two patient groups showed statistically significant differences in the following symptoms: erythema nodosum, aphtous stomatitis (prevalently recorded in patients with CD), pyoderma gangrenosum, primary sclerosing cholangitis and thromboembolic events (more frequently presented in patients with UC) (Table 8).

TABLE 7.
INTESTINAL COMPLICATIONS, DISTRIBUTED BETWEEN PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

Symptoms	Ulcerative colitis Number (%)	Crohn's disease) Number (%)
Massive bleeding		
Yes	6 (2.8)	3 (1.7)*
No	210 (97.3)	177 (98.3)
Toxic megacolon		
Yes	5 (2.3)	0 (0.0)*
No	212 (97.7)	180 (100)
Intestinal perforation		
Yes	2 (0.9)	12 (6.7)*
No	215 (99.1)	168 (93.3)
Carcinoma of the colorectum		
Yes	6 (2.8)	2 (1.1)*
No	211 (97.2)	179 (99.4)
Fistula		
Yes	0 (0.0)	24 (13.3)*
No	217 (100)	163 (90.6)
Abscess		
Yes	0 (0.0)	20 (11.1)*
No	217 (100)	164 (91.1)
Ileus		
Yes	0 (0.0)	25 (13.9)*
No	217 (100)	155 (86.1)
Operative treatment		
Yes	14 (6.5)	39 (21.7)*
No	203 (93.5)	141 (78.3)

* χ^2-test <0.001

TABLE 8.
EXTRAINTESTINAL COMPLICATIONS, DISTRIBUTED BETWEEN PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

Complications	Ulcerative colitis Number (%)	Crohn's disease Number (%)	p
Arthropathy			
Yes	33 (15.2)	29 (16.1)	>0.05*
No	184 (84.8)	151 (83.9)	
Sacroiliitis			
Yes	13 (6.0)	12 (6.7)	>0.05†
No	204 (94.0)	168 (93.3)	
Erythema nodosum			
Yes	15 (6.9)	16 (8.9)	<0.05†
No	202 (93.1)	164 (91.1)	
Pyoderma gangrenosum			
Yes	5 (2.3)	0 (0.0)	<0.05†
No	212 (97.7)	180 (100)	
Aphtous stomatitis			
Yes	20 (9.2)	41 (22.8)	<0.05*
No	197 (90.8)	139 (77.2)	
Gallstones			
Yes	21 (9.7)	18 (10.0)	>0.05†
No	196 (90.3)	162 (90.0)	
Renal stones			
Yes	13 (6.0)	10 (5.6)	>0.05†
No	204 (94.0)	170 (94.4)	
Eye inflammation			
Yes	17 (7.8)	12 (6.7)	>0.05†
No	200 (92.2)	168 (93.3)	
Primary sclerosing cholangitis			
Yes	4 (1.8)	1 (0.6)	<0.05†
No	213 (98.2)	179 (99.4)	
Thromboembolic events			
Yes	4 (1.8)	1 (0.6)	<0.05†
No	213 (98.2)	179 (99.4)	

* χ^2-test, † Fisher's exact test

Familiar gathering of IBD was explored by interviewing patients and the controls on first-line relatives having IBD (Table 9).

TABLE 9.
FIRST-LINE RELATIVES REPORTED AS HAVING IBD, IN PATIENTS WITH IBD AND THE CONTROLS

	Patients with IBD	The controls
Have relatives with IBD	20	7
Not have relatives with s IBD	377	993

χ^2-test (with Yates' correction); $p<0.001$

Disscusion

Comments on demographic data analysis

Demographic data analysis showed that sex preferences, according to whether a patient is diagnosed with UC, or CD, have not been found, in spite of slightly prevalent males to females proportion, found in both patient groups (59% for UC and 63.9% for CD) (Table 1). It has been suggested, according to the past experience, that F sex is preferentially associated with the diagnosis of CD, while UC is likely to be slightly more common in males[1]. However, recent studies, performed mostly in areas with fastly increasing incidence of IBD, show rather variable results[15,17,18]. In the recently performed study, in V-S County, sex preferences, according to the type of diagnosis of IBD, also have not been found[19]. Taken together, it seems that sex preferences, in relation to the type of diagnosis of IBD, might be only secondary to differences in lifestyles between men and women, but this statement needs further confirmation.

In this patient sample, patients diagnosed with UC were, in average, significantly older, than patients diagnosed with CD (Figure 1). More precisely, the majority of patients with CD were in the age range from around 20 to less then 50, while patients with UC were mostly placed within the age range less then 30 to around 60, the results showing a ten-year difference in the age range between the groups (Figure 2). Evidence from the literature indicates earlier time of disease occurence for CD, than for UC, the factor that may influence differences in the average age of patients with UC and CD, in our results[17,18,20]. Results from the recent epidemiologic study, performed in V-S County, also indicate older average age for patients with UC, than for those with CD, with the note that for patients with CD, two age peaks have been recorded, one in younger and the other in the middle aged groups[19]. It is possible that observed differences in the average age, between patients with UC and CD, in this study, are in the background of other differences, found to exist in patients demographic data, including those related to the marital status, level of education, the employment status and the resident status (Table 1). As in the study from V-S County, in Zadar County, there was also higher percentage of immigrants among patients with UC, than among patients with CD, indicating possible role of the immigrant status as a risk factor for UC[19]. This hypothesis is also supported by the results of epidemiologic studies performed on migrant populations all around the world[21,22].

Comments on the incidence and prevalence data

According to our results, in Zadar County, in the last decade, 2000–2010, there was the constant increase in the incidence and prevalence rates for both, UC and CD (Figure 3 and 4). Although both diseases had almost the same average incidence rate (8.2 and 8.4), graphical presentation indicated different time-trends for a particular of two diseases (Figure 3). Based on the graphical presentation, the incidence rates started to rise in 2002. Until 2005, UC showed a continuous course, while in the case of CD, the course was rather scattered. The incidence rates for UC exceeded those for UC. In the period from 2006 to 2010, this trend reverted to a domination of CD over UC (Figure 3). These described time-trends can be explained by the process of intensive migration, taking place in Zadar County in years after the War in Croatia (1991–1997). Namely, psycho-social stress and bad lifestyles, together with fast demographic changes, in the long post-war period, could accelerate the occurence of IBD, during the period 2002–2005, after a short period of latency, 2000–2002 (Figure 3). After the year 2006, there was a new wave of acceleration in the occurence of IBD, especially emphasized in the case of CD, probably due to the process of globalisation. Another contributing factor could be due to the improvements in the endoscopic procedures and health care in general, in the last decades[23]. This explanation is also supported by the graphical presentation of the time-trends in prevalence rates, showing the similar time-points of acceleration, that is, in the years 2004 and 2007 (Figure 4). Similar time-trends in the incidence and prevalence rates of IBD, although at a lower level, and with the same critical time-point, in the year 2006, we could observed in the study recently conducted in V-S County[19]. Observations, made in this study, we provided with the same explanations as are these we are now using in the case of Zadar County[19].

Increasing incidence and prevalence rates of IBD, with the predominant participation of UC over CD, place Zadar County, similar to what was seen for V-S County, into a group of developing areas of Europe[19]. There are also some exceptions to this comparison. As visible on the graph, Figure 3, more steepy increase in the incidence rates for CD, compared to UC, in the period after the year 2006, is likely to take Zadar County on a step closer to the developed countries of Europe and the world. In terms of that, there is a general consensus that, in developed areas of the world, including North America, Canada and Northern Europe, there is a trend of increase in the incidence of CD and stabilisation, although at a relatively high level, in the incidence of UC[9,15,24,25]. It seems, according to our results, that Zadar County, in relation to the occurence of IBD, is now at that position where some

developed parts of Europe and the world were about two decades ago. Related to this, the results of the European IBD Collaborative Study (1991–1993) reported, for the developed Northern parts of Europe, incidence rates for CD of 7.0, that is similar to the average incidence rate of 8.4, estimated for Zadar County, for the period 2000–2010[9]. That some other, specific factor can operate locally, in Zadar County, it is illustrated by the fact that the incidence rates for CD are yet comparable to those recorded in the developed areas of Europe, while the corresponding data for UC are still considerable bellow the level of the developed countries (6.2 against 11.8), indicating more speedy rise in the incidence rates for CD than for UC[9]. Otherwise, the incidence rates for CD that exceed those for UC can only be a marker of very fast development of the Zadar Region. That Zadar Region is not an isolated example in this sense, it can be supported by the similar reports coming from other minor surroundings in Europe, such as the Northern France, or even the Southern Greek[26,27].

In favour to the hypothesis that the observed time--trends for UC and CD, in Zadar County, follow the West to East gradient pattern and rapidly developing areas patterns, rather than the North to South gradient pattern, can also be supported by our results arised from the comparison of all three counties, including also P-G and V-S Counties, in which the epidemiologic studies have already taken place (Table 2–4). However, this comparison has a limitation that includes the restricted time of the overlap between the data; that means, the analysis was done for the early period, 2000–2004, while data comparison for the second, more dynamic period, 2006–2010, is missing. Yet, available data implicate P-G County as the most developed one, based on the highest prevalence rates for both, UC and CD (84.9 and 83.7, respectively). Zadar County is likely to be classified, then, as the rapidly developing area, as its prevalence rate for UC, but not for CD, is approaching that of P-G County (Table 4).

Our results of the comparison of the incidence data, among the counties, can also contribute in favour to the hypothesis of Zadar County as a rapidly developing area (Tables 2 and 3). In this sense, and according to the known pattern for developing areas, the average incidence rate for UC, in Zadar County, exceeds that reported for P-G County (6.2/4.6), while the average incidence rate for CD is slightly bellow that of P-G County (5.2/6.5), with the note that these data are related to the period when the incidence rates for CD have not started yet to rapidly rise (Tables 2 and 3, Figure 3). In line to this provided explanation for Zadar County as a rapidly developing area, experiences of a large-scale indicate that, in developing areas, the increase in incidence of UC precedes the increase in incidence of CD. In developed countries, there is the turning on, from the domination of UC towards the higher incidence of CD[1].

In comparison to P-G and Zadar counties, V-S County is still keeping at the low-level of the incidence and prevalence rates for IBD, similar to some other developing areas in Eastern Europe[11,12]. Moreover, data for V-S County are far bellow those for Zadar County, although V-S County is located in the northern part and Zadar County in the southern part of Croatia. This fact strongly argues against the existence of the North to South gradient, at least in our country.

Comments on the analysis of symptoms, signs and phenotypes

Our results indicate longer duration of symptoms and signs prior to the diagnosis, in patients with CD (an average 6.6 months), in comparison to patients with UC (an average 3.5 months) (Figure 5). These results are similar to what has recently been reported for V-S County and what is cited elsewhere in the literature, indicating the problem of a delay in diagnosing CD as one of a large scale[28,29]. This may be associated with the obscure localisation of CD in the terminal ileum, differences in the pathologic processes between CD and UC and, accordingly, in clinical manifestations of these two diseases. Related to this, our results indicate more general symptoms as the first clinical manifestations of CD, in contrast to the local, intestinal symptoms which are likely to correlate with the onset of UC (Table 5). These general symptoms, in patients with CD, as other authors also state, are therefore difficult to observe, until some more pronounced symptoms, later during the course of the disease, do occur, such as anemia, or weight loss[29]. Another contributing factor to a longer duration of symptoms before the diagnosis, in patients with CD, may be younger age at disease onset, compared to UC. In Zadar County cohort, it is clearly illustrated with the average age of 31.9 years, in patients with CD, in contrast to 42.2 years, in patients with UC (Figure 2). Namely, as we have already concluded, in the study conducted in V-S County, young patients might be less sensitive in recognising early disease symptoms[28].

An alternative explanation is that clinical presentation of IBD may be a consequence of the extent of a disease. In this patient group with UC, the most common phenotypes, although the distribution not reaching the statistically significant difference, were E3 (extensive colitis and pancolitis) and E2 (the rectum and the left colon) (Figure 6). These results, indicating rather extended type of disease, even indirectly, suggest a long disease duration. Namely, as according to the evidence, the proximal extent of inflammation has a tendency to progress over time[30]. In terms of that, results of some studies indicate that after 20 years of disease duration, a large proportion of patients are likely to acquire the extended type of disease, in the form of pancolitis[31]. Another explanation may be that, in this patient group, biologic treatment, known to strongly modulate the natural course of the disease, have might been missing[32]. Based on this discussion, however, it becomes clear that clinical presentation of the Zadar County UC cohort, with 4–7 bloody, slimy stools per day, that correspond with mild to moderate disease severity grade, can not add much information to the prognosis, because the evidence says that the disease activity shows a tendency to decrease over time[33,34].

With respect to patients with CD, the most common phenotype, according to the Montreal's classification, corresponds with young adult age (17–40 years), noncomplicated (inflammatory) behaviour and disease localisation in the terminal ileum, or the ileocolon (Figure 7, Table 8). Based on the world experience, the prevalent localisation of CD, at the time of diagnosis, is the ileocolonic disease, as it has been also reported for the cohort from V-S County[28,30,35]. The bias towards isolated small bowel disease, in the Zadar County patient group, is not likely to reflect their average younger age, compared, for example, to the cohort from V-S County (around 31 and 41 years, respectively), as the localisation of CD, unlike disease behaviour, is likely to maintain stable over time[30,36]. Related to this fact, noncomplicated (inflammatory) behaviour of CD, dominating in our sample, and presented mainly with general symptoms, is more likely to reflect younger average age at disease onset, compared to the cohort from V-S County, where mainly the stricturing disease behaviour (phenotype B3), indicating longer disease duration, has been recorded[28]. The question which seeks for an answer might be, whether the rapidly increasing incidence rates of CD, in fastly developing areas such Zadar County is likely to be, could precipitate the disease gathering in younger age agroups?

Comments on complications

In line with what was expected according to the natural course of IBD, intestinal complications requiring surgical treatment, including perforation, fistula, abscess and ileus, have been typically observed in patients with CD, while in patients with UC, they have been almost completely absent (Table 9). Yet, the percentage of patients with CD who needed surgical treatment (21,7%) did not reach the levels cited in some large epidemiologic studies[37,38]. For this disproportion, many factors can be accounted for, including changes in the natural course of this disease over time, improvements in diagnostics and treatment, or some specific factors which may affect the natural course of the disease, opperating in some local surroundings, as Zadar County is. Or, simply, lover level requirements for surgical treatments, in this patient group with CD, can be associated with their relatively younger average age.

In contrast to patients with CD, patients with UC, in our sample, are more likely to develop complications which are due to overwhelming inflammation, such as massive rectal bleeding and toxic megacolon (Table 9). According to our results, also, colorectal cancer, a known late-onset complication of IBD, is, as expectedly, more pronounced, although at the low level, in relation to UC (Table 9)[39].

With respect to the extraintestinal complications, patients in this sample were mainly presented with immunologically mediated complications, except for tromboembolic events, found in patients with UC. These findings are likely to indicate close associations of these complications with chronic inflammation (Table 10)[39]. When comparisons with the results of the study from V-S County had been made, it became clear that, in patients with CD, from Zadar County, unlike to those from V-S County, usual skin disorders, including aphtous stomatitis and erythema nodosum, were the prevailing extraintestinal signs, while there were no clinically more strongly defined entities, such as ankylosing spondylitis[28]. The difference is probably reflecting differences in average age and disease duration between the two groups, or in some other, genetical, or environmental factors[39]. That congenital factors, either genetical, or acquired ones, gathered within some families, may affect the natural course and clinical presentation of IBD, it is supported by the results of this study, showing significantly higher number of persons with IBD among first-order relatives of patients, compared to the controls (Table 11).

Conclusions

Croatia, with its unique geogaphical location, at the border between the East and the West of Europe, and by encompassing the northern, continental, and the southern, coastal parts, is likely to be an ideal area for testing the West to East and the North to South gradient hypotheses of IBD spreding. In addition, Croatia has experienced fast demographic and social changes in the recent past. As our results indicate, here, on the relatively small surface area, great changes in time-dependent trends in the incidence and prevalence rates of IBD, in the last two decades, can be noticed. Based on the comparative analysis which included three differently positioned and unequally developed counties, Primorsko-Goranska, Zadarska and Vukovarsko-Srijemska, it can be concluded that the pattern of the epidemiologic changes of IBD is likely to strictly follow the rate of the economic and social development of a particular area and, in some way, can serve as a marker of the intensity of these changes. Once again, this paper indicates towards the values of performing epidemiologic and population-based studies for assessing, not only changes in occurence of IBD, but also changes in their natural courses and risk factors.

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EPIDEMIOLOGIJA I KLINIČKE ZNAČAJKE UPALNIH BOLESTI CRIJEVA U ZADARSKOJ ŽUPANIJI, HRVATSKA

S A Ž E T A K

Prikazani su rezultati retrospektivne populacijske studije, 2000–2010, o upalnim bolestima crijeva, ulceroznom kolitisu (UC) i Cronovoj bolesti (CD), za Zadarsku županiju, te uspoređeni s podacima iz svijeta i komparativnim podacima za Primorsko-Goransku i Vukovarsko-Srijemsku županiju. Prosječne stope incidencije (na 100 000) su iznosile 8.2 i 8.4, za UC i CD, ponaosob. Stope prevalencije, na kraju razdoblja praćenja, su iznosile 133.9 za UC i 111 za CD. Za obje bolesti je registriran stalni rast stopa incidencije, za CD izrazitije u drugoj polovini vremena praćenja, 2006–2010. Stope prevalencije su kontinuirano rasle za obje bolesti, s tim da su vrijednosti za UC prevazilazile one za CD. Rezultati dobiveni usporedbom podataka između županija govore u prilog hipotezi o Zadarskoj županiji kao o području koje se brzo razvija, a protiv su postojanja Sjever-Jug gradijenta između Vukovarsko-Srijemske i Zadarske županije.