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Alimentary Tract

Epidemiology of inflammatory bowel disease in the Republic of San Marino: The "EPIMICI – San Marino" study

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ABSTRACT

Background: The burden of Crohn's disease (CD) and ulcerative colitis (UC) has never been estimated in the Republic of San Marino, the third smallest nation of the world.
Aims: To assess the occurrence and clinical features of CD and UC in San Marino during the last 35 years.
Methods: We retrospectively evaluated the prevalence, incidence, and main clinical aspects of CD and UC from 1980 to 2014, crossing data from various sources.
Results: Prevalence rates (per 100,000) on December 31, were 241 for CD (263 in males and 220 in females) and 311 for UC (370 in males and 255 in females). The specific incidence of UC steadily increased from 4.6 (95% CI: 1.5–10.6) in 1980–1984 to 12.4 (95% CI: 7.6–19.1) in 2010–2014; CD incidence showed a higher proportional increase, from 1.8 (95% CI: 0.2–6.6) in 1980–1984 to 17.9 (95% CI: 12.0–25.7) in 2010–2014. The main clinical features of CD and UC (activity and location at diagnosis, extra-intestinal manifestations, disease progression overtime, therapies, and hospitalizations) were analyzed.
Conclusions: This study provides the first epidemiological report on CD and UC in San Marino, showing specific traits and overall higher prevalence and incidence rates than previously reported in neighbor Areas.

1. Introduction

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the digestive tract, resulting from a loss of homeostasis between intestinal immune system and gut microbiota, in genetically-predisposed individuals [1]. Inappropriate mucosal immune responses, due to disruption of the epithelial barrier, separating microorganisms from underlying tissues, and/or dysregulated tolerance to the intestinal microbiota, likely contribute to the development and perpetuation of IBD [2,3]. IBD peak incidence occurs in the second or third decade of life [4] and consequently affects the quality of life and the working productivity of patients, who are required to follow long-term treatments, tight medical controls, and, in some cases, hospitalizations and surgery [5].

IBD is classically associated with industrialization, although recent data reported accelerating incidence in newly industrialized Countries and stable incidence in Western Countries, where burden remains high, as prevalence surpasses 0.3% [6,7]. The advancements in diagnostics and the better understanding of IBD pathophysiology and natural history have also had an impact on the epidemiology of IBD, since they have likely contributed to increase UC and CD prevalence. However, IBD epidemiological data are conflicting, with a wide range of estimates, within and between geographic areas [7,8].

The Republic of San Marino is the third smallest country of the world, located in the northeastern part of the Italian peninsula. San Marino's Healthcare System has many peculiar aspects, such as a universal free-of-charge coverage, a single Gastrointestinal Disease Center within the State Hospital, which works in synergy with the Primary Care System, an electronic database

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where all healthcare data are recorded. San Marino can represent a model for epidemiological population-based studies; indeed, in large population studies many confounding factors affect the analysis, while a population-based study on a small community, with homogeneous socio-demographic characteristics, could make epidemiological data more reliable. Interestingly, in San Marino the evaluation of epidemiological features in different gastrointestinal and extra-intestinal diseases (*i.e.*, colorectal cancer, celiac disease, multiple sclerosis, and hypertension) has shown specific data, different when compared to close areas in Italy [9–12].

In the present study, which we named "EPIMICI – San Marino" [for EPIdemiology of IBD (MICI, "Malattie Infiammatorie Croniche Intestinali", Italian language) in the Republic of San Marino], we explored the epidemiology of IBD in San Marino, from 1980 to 2014. In particular, primary aim of our study was to evaluate IBD prevalence, incidence, and incidence trends. The secondary objective was to depict the main clinical features of CD and UC in this Country, including activity and location at diagnosis, extra-intestinal manifestations, disease progression overtime, therapies, and hospitalizations.

2. Material and methods

2.1. Data source

In San Marino, all inhabitants have free-of-charge public sanitary assistance and healthcare data are recorded in an electronic clinical records database (CRD). The population is ethnically homogeneous, mainly composed by Caucasians, with little migration. The State Hospital of San Marino provides health assistance of first and second level for all inhabitants. For third level health assistance, patients are referred to selected Italian Centers.

In our study, we crossed data from CRD with data extracted by SAS software from the following sources of information: hospital discharge records, health administrative services, and death certificate registry.

2.2. Data collection and subjects

IBD patients were identified among all San Marino's inhabitants, searching from 1980 to 31 December 2014, for the following diagnosis: "ulcerative colitis", "Crohn's disease", "aphtous ileitis", "regional enteritis", and "inflammatory bowel disease". Duplicated cases were excluded.

Patients with confirmed gastrointestinal infectious diseases were excluded. For each identified patient, clinical, radiological, endoscopic and histology reports were reviewed to confirm the IBD diagnosis. The following data were also collected: sex, date of birth, IBD familiarity, smoking habits, year of diagnosis, clinical presentation (diarrhea, constipation, mixed bowel habits, tenesmus, abdominal pain, bowel obstruction, rectal bleeding), extra-intestinal manifestations (ocular, cutaneous, articular and hepatic), C-reactive protein (CRP) and hemoglobin levels, disease location (according to Montreal Classification), endoscopic activity [according to Mayo Endoscopic Score [13] and Simplified Endoscopic Score for Crohn's Disease (SES-CD score) [14], for UC and CD respectively], hospitalizations (number, hospital stay length, hospital ward), therapy at diagnosis and need for therapeutic interventions and adjustments during follow up (steroids, antibiotics, immunosuppressive drugs, biologics, surgery), cancer occurrence, date and cause of eventual death.

2.3. Statistical analysis

All data of interest were reported on Microsoft Excel worksheet. Age-standardized (European population) rates per 100,000 inhabitants were calculated separately for IBD, UC, and CD.

To calculate prevalence and age-standardized prevalence of IBD in San Marino, we used population data of each corresponding year, provided by the Authority for Health, Socio-Health and Socio-Educational Services of San Marino. In particular, the prevalence rate was calculated using all subjects who were alive and residing in San Marino on December 31, 2014 as the denominator. For incidence rates the sums of the resident population on each corresponding year were used as the denominators. The prevalence was expressed as the number of patients with IBD per 100,000 persons.

The incidence was expressed as the number of subjects with new diagnosis of IBD per 100,000 persons per year. Data were reported as mean percentage and 95% confidence intervals (95% CI).

For descriptive statistics, proportions were calculated for categorical variables, while mean and standard error (SE) and/or median/interquartile range (IQR) were used for continuous variables.

Differences between groups were analyzed by chi-square test for categorical data. A p value of <0.05 was considered statistically significant.

Data analyses were performed using Stata software (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP) and Real Statistics Resource Pack software (Release 3.5; Copyright 2013–2015 Charles Zaiontz; www.real-statistics.com).

2.4. Ethics

The study protocol was approved by the local Ethical Committee (Comitato Etico per la Ricerca e la Sperimentazione-CERS, Repubblica di San Marino, prot. n. 43/2015/CERS) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

3. Results

3.1. IBD epidemiology in San Marino

San Marino inhabitants in 1980 were 21,537. At the end of 2014, the total population of San Marino was 32,789 (16,656 females and 16,133 males), with a population density of 535.8 inhabitants/km^2, higher than the neighbouring areas (387.96 for the province of Rimini) [15].

In the evaluated period of time (1980–2014), 188 IBD cases were found; of those, 105 were diagnosed with UC (62 men and 43 females) and 83 with CD (45 men and 38 females). Average age at diagnosis was 39 y.o. for UC (IQR 26–46) and 40 y.o. for CD (IQR 27.5–52). Male-to-female ratio was 1.44 for UC and 1.18 for CD.

At the end of study, 181 IBD patients (102 UC and 79 CD cases) were alive and living in San Marino. The standardized prevalence rate (per 100,000) of IBD was 552; the prevalence rate for sex was 633 per 100,000 in males and 475 per 100,000 in females. The prevalence rate (per 100,000) for CD was 241 (263 in males and 220 in females). As expected, the UC prevalence rate (per 100,000) was higher than CD (311) and showed a larger difference between genders (370 in males and 255 in females).

As for age distribution, most of IBD patients' age ranged between 30 and 70 years, with a peak for the 50–59 decade. In the population aged less than 20 years, IBD prevalence was very low, especially in females; as age increased, the prevalence increased, with the highest rates in the age-class of 50–59 years (598/100,000 for UC

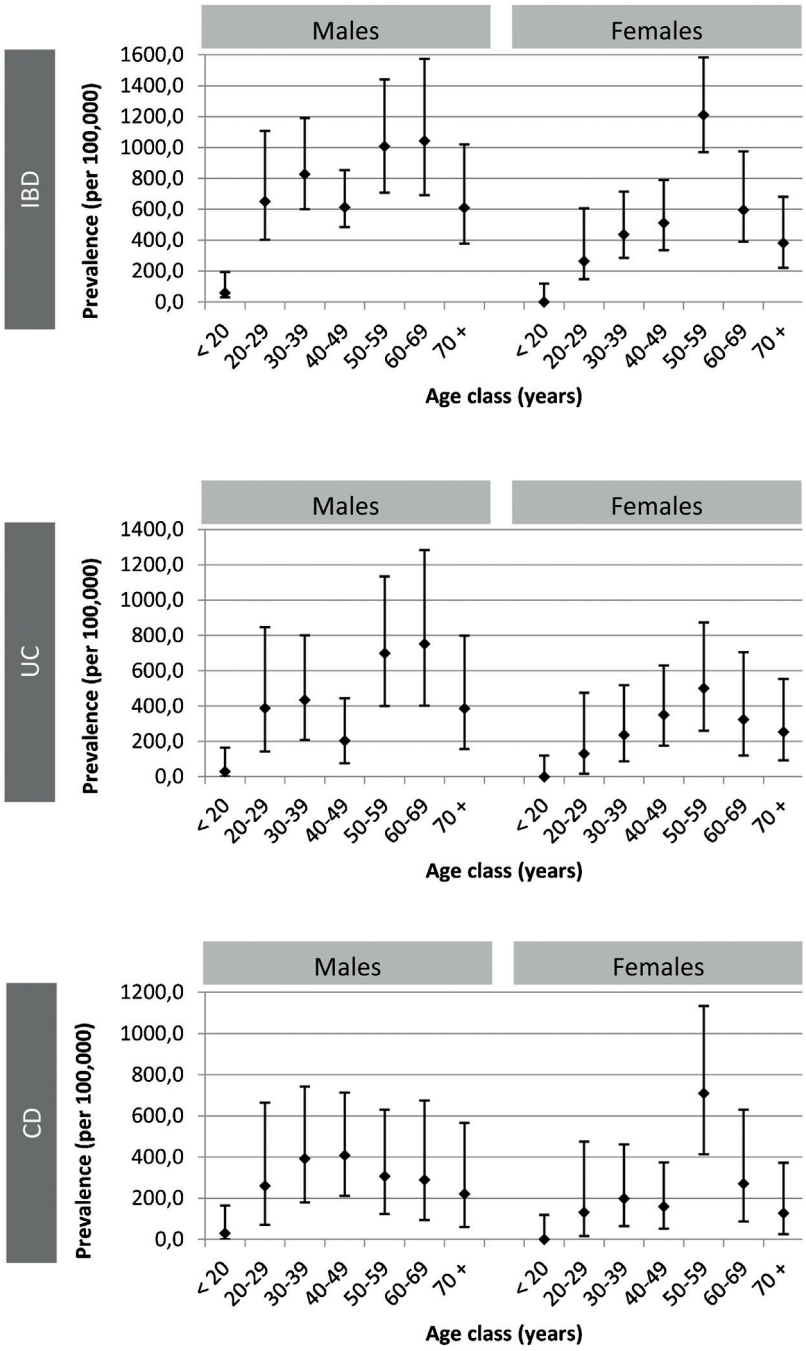
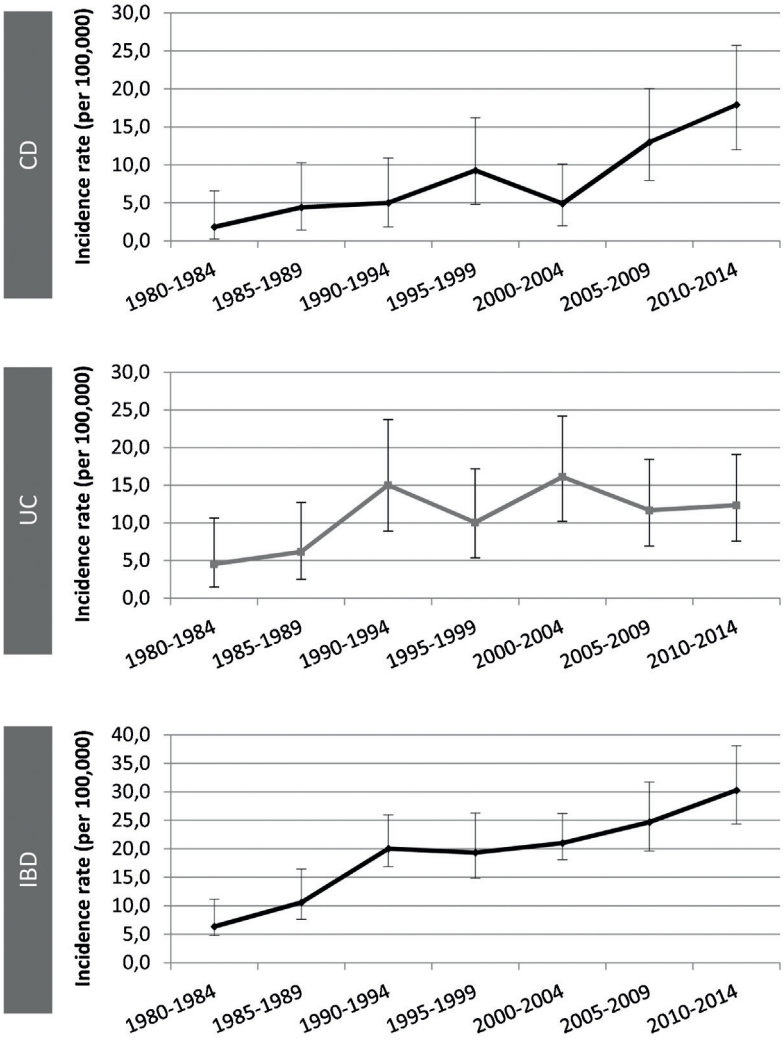


Fig. 1. Standardized prevalence rate (per 100,000) of inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD), stratified for age-classes and sex, at the end of study.

and 513/100,000 for CD, respectively). UC prevalence increased steadily with age, up to the 7th decade of life. Of note, a reduction of UC prevalence was observed for age-class 40–49 years, only in males; the highest prevalence was observed in the 60–69 years old age-class in males (753/100,000) and in the 50–59 years old age-class in females (501/100,000). Similarly, CD prevalence increased with age, peaking in the 50–59 years old age-class for females (710/100,000) and in the 40–49 years old age-class for males (409/100,000). Prevalence rates by age and gender are depicted in Fig. 1 (see also Supplementary Table S1 in the online version at DOI: 10.1016/j.dld.2018.08.016).

During the 1980–2014 period, IBD incidence progressively increased, from 6.4/100,000 in 1980–1984, up to 30.3/100,000 in 2010–2014. The incidence of UC steadily increased from 1980 to 1984 to 2005–2009, and then remained stable between 2010 and 2014. Conversely, a further and consistent increase in CD incidence was observed in the last 5 years (Fig. 2). Focusing on the last five years under analysis, the age-specific incidence for UC peaked in the age class of 20–29 years (25.4/100,000). As for the incidence in children and adolescents, it was very low, especially in females, and no new diagnoses were made before 10 years of age. UC incidence stratified for sex was 17.2/100,000 in males and 7.0/100,000 in females. As for CD, the highest age-specific incidences from 2010 to 2014 were found in two different age classes: 30–39 years (35.7/100,000) and 50–59 years (30.1/100,000). Stratifying for sex, the incidence was higher in male CD patients, except for the 20–29 age class. A similar trend for males and females was observed, with a common late peak in the 50–59 decade and an early peak, which



Year	5-year incidence rate per 100,000								
	Crohn's disease	95% CI		Ulcerative colitis	95% CI		Inflammatory bowel diseases	95% CI	
1980-1984	1,8	0,2	6,6	4,6	1,5	10,6	6,4	2,6	13,13
1985-1989	4,4	1,4	10,3	6,2	2,5	12,7	10,6	5,5	18,49
1990-1994	5,0	1,8	10,9	15,0	8,9	23,7	20,0	12,8	29,81
1995-1999	9,3	4,8	16,2	10,0	5,4	17,2	19,3	12,5	28,53
2000-2004	4,9	2,0	10,1	16,1	10,2	24,2	21,0	14,2	29,99
2005-2009	13,0	7,9	20,1	11,7	6,9	18,5	24,7	17,5	33,85
2010-2014	17,9	12,0	25,7	12,4	7,6	19,1	30,3	22,4	40,01

Fig. 2. Incidence rates (per 100,000) [+95% confidence intervals, 95% CI] of Crohn's disease (CD), ulcerative colitis (UC), and inflammatory bowel disease (IBD), in quinquennial, from 1980 to 1984 to 2010 to 2014.

occurred sooner in females (20–29 years age-class *versus* 30–39 in males). UC and CD incidence rates by age and gender, for the last five years under analysis, are depicted in Fig. 3.

3.2. UC-specific clinical characteristics

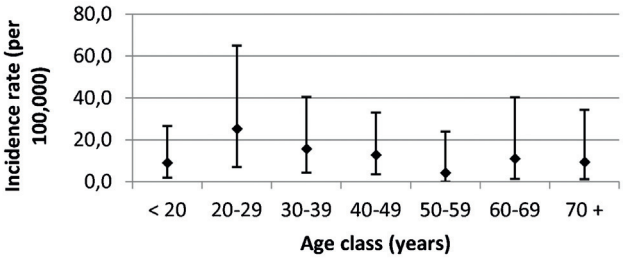
Eleven percent of UC patients had a first-degree relative with IBD; 10% of UC cases were active smokers at the time of diagnosis, while 6% were former smokers.

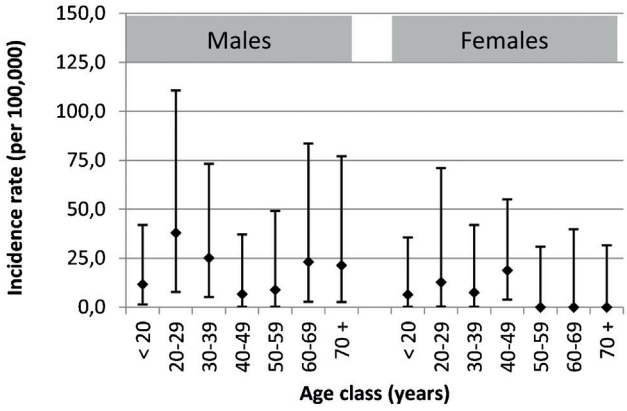
Disease location and endoscopic disease severity at diagnosis are depicted in Fig. 4. UC location was most frequently limited to the left colon and rectum and most of patients presented with moderate activity of disease.

As for clinical presentation at diagnosis, 86% of patients reported bloody stools, 21% abdominal pain, up to 55% of cases suffered from diarrhea associated with either breeding, tenesmo, and/or abdominal pain. CRP was elevated in 45% of patients; 11% of cases were anemic.

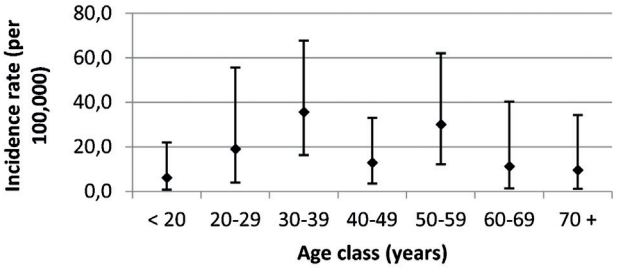
The most common therapy at diagnosis was mesalazine alone or in combination with antibiotics (66%), followed by mesalazine and/or antibiotics plus steroids (34%). None of the UC patients received surgical treatment, or immunosuppressants, or biologics, during the first 3 months after diagnosis. Most of the patients (96%) was left on maintenance treatment with mesalazine monotherapy. In the whole follow up period, 70% of UC patients required a treatment adjustment. Of those, 100% needed one or more

	UC Age class	Incidence rate	95% CI	
UC	< 20	9,1	1,9	26,7
	20-29	25,4	6,9	65,0
	30-39	15,8	4,3	40,6
	40-49	12,9	3,5	33,1
	50-59	4,3	0,1	23,9
	60-69	11,2	1,4	40,4
	70 +	9,5	1,2	34,3
	Total	12,0	7,3	18,5
Male	< 20	11,6	1,4	41,9
	20-29	37,9	7,8	110,7
	30-39	25,1	5,2	73,3
	40-49	6,7	0,2	37,1
	50-59	8,8	0,2	49,1
	60-69	23,2	2,8	83,6
	70 +	21,3	2,6	77,1
	Total	17,2	9,4	28,8
Female	< 20	6,4	0,2	35,6
	20-29	12,8	0,3	71,1
	30-39	7,5	0,2	42,0
	40-49	18,8	3,9	55,0
	50-59	0,0	0,0	30,9
	60-69	0,0	0,0	39,8
	70 +	0,0	0,0	31,6
	Total	7,0	2,6	15,3





	CD Age class	Incidence rate	95% CI	
CD	< 20	6,1	0,7	22,0
	20-29	19,0	3,9	55,6
	30-39	35,7	16,3	67,7
	40-49	12,9	3,5	33,1
	50-59	30,1	12,1	62,0
	60-69	11,2	1,4	40,4
	70 +	9,5	1,2	34,3
	Total	17,4	11,6	24,9
Male	< 20	11,6	1,4	41,9
	20-29	12,6	0,3	70,3
	30-39	58,5	23,5	120,5
	40-49	13,3	1,6	48,1
	50-59	35,3	9,6	90,2
	60-69	11,6	0,3	64,5
	70 +	21,3	2,6	77,1
		23,3	14,0	36,4
Female	< 20	0,0	0,0	23,6
	20-29	25,5	3,1	92,2
	30-39	15,1	1,8	54,4
	40-49	12,5	1,5	45,3
	50-59	25,2	5,2	73,5
	60-69	10,8	0,3	60,2
	70 +	0,0	0,0	31,6
		11,7	5,6	21,5



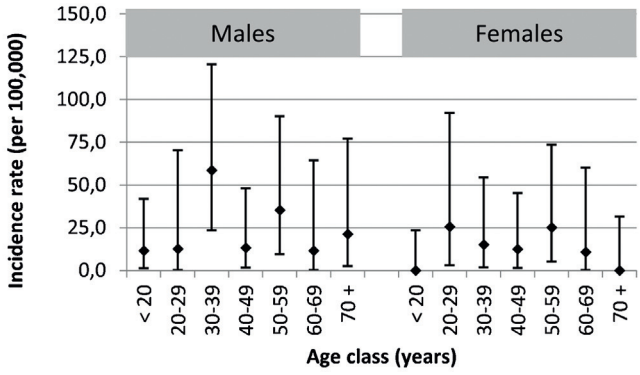


Fig. 3. Incidence rate (per 100,000) [+95% confidence intervals, 95% CI] by age and sex of ulcerative colitis (UC) and Crohn's disease (CD), between 2010 and 2014.

courses of steroids, 28% received immunosuppressants, 5% underwent surgery (3 patients for refractory UC and 1 patient for colon cancer development), and 8% was treated with biologics (anti-TNF).

Thirty-eight percent of patients needed hospitalization, with a mean hospitalization rate of 1.75 (SE 0.22) per patient, and a mean hospital stay of 12.78 (SE 1.02) days per hospitalization (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.dld.2018.08.016). Eighty-four percent of patients were admitted to the Medical ward, while 16% were hospitalized in the Surgical one.

During follow-up, in 35% of cases the disease showed progression in terms of location (from E1 to E2/E3 or from E2 to E3), mainly within the first decade from diagnosis [mean progression time 9.17 years (SE 1.19)]. Moreover, 16% of patients developed extraintestinal manifestations; of those, 67% were articular, 33% cutaneous, 16% ocular and 7% hepatic.

Overall, disease activity improved overtime, and, at the latest follow-up endoscopy, 40% of patients was in endoscopic remission (Mayo score 0), while 60% had active disease (23% Mayo 1; 28% Mayo 2 and 9% Mayo 3).

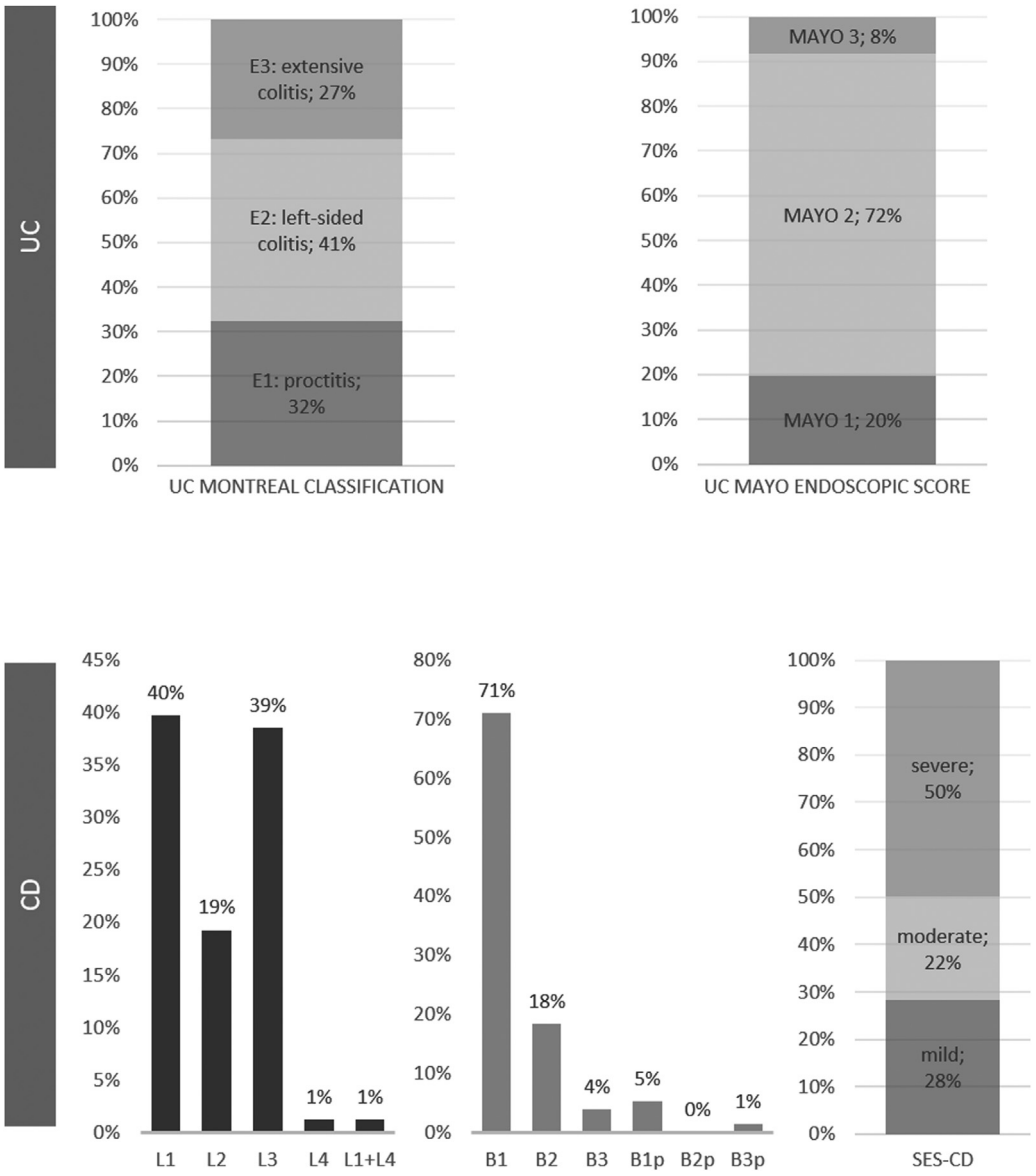


Fig. 4. IBD Disease classification at diagnosis: Montreal Classification and Mayo Endoscopic Score Classification for ulcerative colitis (UC, *upper row*); Montreal Classification and SES-CD for Crohn's disease (CD, *lower row*).

From 1980 to 2014, 13 UC patients developed cancer (11 extraintestinal tumors and 2 colon cancers). At the end of study, 3 male patients had died; in particular, one patient died from colon cancer (14 years after UC diagnosis), another died from pancreatic neoplasia and the third one died from Parkinson's Disease.

3.3. CD-specific clinical characteristics

The percentage of CD patients with IBD familiarity was 7%, similar to that for UC (11%, $p \geq 0.05$). We found more active smokers among CD patients than UC patients (27% versus 10%, $p < 0.05$) at diagnosis. Conversely, the frequency of previous smokers did not significantly differ between CD and UC (13% and 6% respectively, $p \geq 0.05$).

CD clinical phenotype at diagnosis is depicted in Fig. 4. Most frequently, CD presented as ileal or ileo-colonic disease, non stricturing-non penetrating. Endoscopic disease severity was mostly severe or moderate.

As for clinical presentation at diagnosis, 64% of patients suffered from diarrhea and/or abdominal pain, while mixed bowel habit or constipation with or without abdominal pain were reported by 20% of cases. Rectal bleeding was observed in 27% of patients; 8% of cases presented with bowel obstruction. CRP was elevated in 72% of patients; 18% of cases also presented with anemia.

The most common therapy at diagnosis was steroids alone, or in combination with mesalazine and/or with antibiotics (46%), followed by mesalazine and/or antibiotics (42%). 5% of patients received surgical treatment at diagnosis (3 cases for stricturing disease and 1 for colon cancer) while only a minority of them was treated with enteral nutrition (1%), azathioprine (1%), or refused treatment (1%). None of CD patients received biologics within 3 months from diagnosis. In the whole follow up period, 77% of CD patients required a treatment adjustment. Of those, 83% needed one or more cycles of steroids, 34% received immunosuppressants, 30% underwent surgery (of those, 47% within one year from diagnosis), and 23% was treated with biologics (anti-TNF).

Forty-six percent of patients needed hospitalization, with a mean hospitalization rate of 2.05 (SE 0.21) per patient, and a mean hospital stay of 9.19 (SE 0.73) days per hospitalization (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.dld.2018.08.016).

Fifty-three percent of hospitalizations were in the Medical ward, while 47% were in the Surgical one.

During follow-up, 27% of patients showed disease progression, mainly within the first decade from diagnosis. The progression affected disease location (transition from L1 to L3, or from L2 to L3) in 65%, and behavior (transition from B1 to B2 and/or B3, from B2 to B3, from B3 to B2) in 50% of cases. Thirty-five percent of patients also developed perianal manifestations during the first decade of follow-up. Moreover, 22% of patients was affected by extraintestinal manifestations; of those, 88% were articular, 38% cutaneous and only 6% hepatic. There was not a statistically significant difference between CD and UC, regarding frequencies of extraintestinal manifestation ($p \geq 0.05$).

Overall, at the latest follow-up visit, 51% of patients was judged as in disease remission (clinical and/or biochemical and/or endoscopic and/or radiological), while 49% had active disease (13% mild; 29% moderate and 7% severe).

During follow-up, 8 patients developed cancer (7 extra-intestinal tumors and 1 colon cancer). At the end of study, 3 male and 1 female patients had died; in particular, one patient died from acute respiratory distress syndrome and 3 patients died from cancer (2 pulmonary neoplasia and 1 Hodgkin lymphoma).

4. Discussion

The knowledge of IBD epidemiology plays a key role to understand IBD pathophysiology [16]. Annual IBD incidence rate, according to the Epidemiological Committee (EpiCom) study (2011 inception cohort), was 14.0/100,000 for Western Europe and 11.6/100,000 for Italy in particular (3.3 and 6.3 per 100,000 for CD and UC respectively) [17]. Available information about time trends in incidence, prevalence and public health impact of IBD in Italy is hampered by a high degree of variability, due to lack of a national registry (except for pediatric patients) and differences in data sources and study design. In several geographic areas, the reported incidence rates range between 2.3 and 15.4 per 100,000 [18–21]. The estimated national incidence (per 100,000) is 3.9 for CD, and 7.2 for UC [22]. However, in a population-based cross-sectional study on administrative data in the Lazio region (Central Italy), Di Domenicantonio et al., reported a prevalence and incidence of IBD in Italy up to 15% higher than previously expected [23]. Very recently, Valpiani et al., published data from the population-based IBD registry in the Area of Forlì (Northern Italy, close to San Marino), between 1993 and 2013. The prevalence rates (per 100,000) for CD and UC were 109.2 and 266.4, respectively and the standardized annual incidence rates (per 100,000) were 12.8 in UC females, 15.7 in UC males, 7.0 in CD females and 5.4 in CD males [24].

San Marino can represent an ideal setting for epidemiological population-based studies. San Marino's social and political trends track closely with those of its larger neighbor, Italy. Most San Marino's inhabitants follow a Mediterranean diet. The main ethnic groups are Italian (71%), native Sammarinese (20%), French (4%), and English (2%). The economy of San Marino relies on tourism, banking, and the manufacture and export of ceramics, clothing, fabrics, furniture, paints, spirits, tiles, and wine. The per capita level of output and standard of living are comparable to those of the most prosperous regions of Italy. The income tax rate is low, about one-third the average European level. San Marino's economy contracted considerably in the last ten years, given the global economic downturn [25].

In San Marino, immigration is regulated by restrictive laws (blood ties, marriage, work). In 2014, net migration rate was 5.28/1000 and 15.3% of the whole San Marino population was represented by foreign persons with residency permit (86% from Italy, 2.6% from Romania, 1.3% from Argentina, 0.9% from Albania) [26].

In the last years, there has been a progressive increase of the average San Marino's population, due to the positivity of both the rate of natural change and the net migration rate. In particular, in 2014, birth rate (per 1000) was 9.02, death rate was 7.69, with a natural change of 1.34/1000. Birth rate was lower in San Marino *versus* the mean European rate, (10.4) but it was higher than the average Italian one (8.5); fertility rate was 1.53. As for the causes of death, cardiovascular disease was at the first place (34.2%), followed by cancer (33.6%) and respiratory disease (9.3%) [27].

As for vaccination policies, mandatory vaccines are against polio, diphtheria, pertussis, tetanus, hepatitis B, haemophilus influentiae type B, measles, mumps, and rubella. In 2014, vaccination rates were satisfactory for polio (83.8%), while they were below the critical value to grant herd immunity for measles–mumps–rubella (69.7%), given the increasing number of objectors in the last years [28].

San Marino is among the first five Countries in the World for life expectancy; in 2014, life expectancy was 81.9 years for men and 86.4 years for women. In the last years, there has been a progressive increase of the ageing index (from 108.19 in 2004, to 123.6 in 2014), since the age structure is regressive, like the neighbouring areas [26].

In our study, we found a prevalence rate (per 100,000) of 241 for CD (263 in males and 220 in females) and of 311 for UC (370 in males and 255 in females). These data are significantly higher, compared with the aforementioned reports. As for incidence rates, from 1980 to 2014 the incidence (per 100,000) of IBD progressively increased, from 6.4 up to 30.3; this was mainly sustained by an augmented CD incidence rate. Indeed, UC incidence increased from 1980 to 1984 to 2005 to 2009, and then remained substantially stable from 2010 to 2014. CD incidence showed a similar trend up to 2010; afterward, a further and consistent increase was observed. Moreover, while the crude incidence rates during the 1980–2014 period were higher in UC than CD, we found an opposite scenario during the 2010–2014 period. The reasons for these differences are unknown and should be further investigated, but they could reflect a change in specific population characteristics and habits in the last years. When compared with the Forlì experience, the trend of incidence increase was confirmed for CD, but not for UC, since Valpiani et al., did not report substantial changes overtime in UC incidence rate. Regarding age-specific incidence rates, we found an overall similar trend for UC, while for CD the peak of incidence occurred later for males *versus* the Forlì study [24]. As for age- and sex-based differences in IBD incidence, our study showed some peculiarities, when compared to the most recent literature [29]. In particular, we confirmed a lower incidence of CD and UC in females compared to males in childhood and adolescence and also after 50 years of age for UC. Similarly, we found an increased incidence of disease in females during child-bearing years, but we observed a female predominance only in the 20–29 age class for CD and in the 40–49 age class for UC.

Overall, our data on IBD prevalence and incidence are higher than expected, when compared to other studies, also from neighbor areas. The interpretation of these results is not straightforward. The peculiarities of San Marino Healthcare System might be responsible, at least in part, for the very high proportion of captured cases.

In concordance with previous reports, we observed a higher percentage of CD patients being current smokers at diagnosis compared to UC patients [30]; in contrast, we did not find significant difference for former smokers between CD and UC. This last result is in agreement with the data from the EpiCom study for Western Europe [17]. As for family history, about 10% of IBD patients had a first degree relative with IBD; no statistically significant differences were found between CD and UC, as reported in literature [31]. Similarly, the frequency of extra-intestinal manifestations was in concordance with previous reports [31].

As for IBD clinical presentation, we found similar results in terms of UC disease extent and CD behavior at diagnosis, compared with the EpiCom study. Conversely, San Marino CD patients had a peculiar location pattern at diagnosis, with more frequent ileal and ileo-colonic involvement and less colonic, isolated upper GI cases and perianal manifestation, than reported elsewhere [17,32].

Initial treatment approach was in line with other studies for UC, while the management of CD had some differences [17], which tended to be leveled out during follow-up, when relapsing and refractory patients underwent progression on the treatment pyramid (i.e., need for surgery within 1 year from diagnosis was 13% in CD patients, in concordance with literature) [17].

Published data on IBD hospitalization rates are extremely heterogeneous [17,18,27,32–34]. In our study, hospitalization rates were lower than we had anticipated, given the long follow-up time. As expected, UC patients were most frequently admitted to the Medical Ward, while CD patients accessed almost equally Medicine and Surgery wards. CD patients underwent more hospitalizations than UC patients did, but the mean hospital stay was shorter for CD than UC patients.

The primary strengths of this study are represented by the universality and consistency of San Marino Healthcare System, the homogeneity of the population under analysis, the long follow-up time. The main limitation was the retrospective nature of the analysis, which did not allow us to collect data regarding quality of life and environmental factors.

In summary, the "EPIMICI – San Marino" study provides the first epidemiological data on the occurrence of IBD in San Marino, showing overall higher incidence and prevalence rates, than those reported in neighbouring areas. Moreover, IBD phenotype at diagnosis in San Marino presents peculiar aspects, and this could partially explain some differences found in the management of CD patients. Many speculations can be made, especially considering the condition of relative isolation that has characterized San Marino in the past years, because of geo-politic reasons. On the other side, it could reflect the efficient index capacity of its universalistic health recording system. Further studies are needed to clarify these findings, and to assess their socio-economic implications.

Conflict of interest

A. Armuzzi has served as a consultant for AbbVie, Allergan, Biogen, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung, Sofar and Takeda; he has also received lecture fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, MSD, Mundipharma, Nikkiso, Otsuka, Pfizer, Takeda, Tigenix and Zambon and he has received research funding from MSD.

E. Leoncini has served as a consultant for Amgen, Baxalta, Grunenthal, Janssen, Novo Nordisk, Otsuka, Pfizer, Roche, Takeda.

Gasbarrini is a member of speakers' bureau of: MSD, Abbvie, Gilead, Alfasigma, Biocure, Actial, Sanofi, Takeda, Dicofarm.

The other authors have nothing to disclose.

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