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Observational Study

**Clinical and epidemiological features of ulcerative colitis patients in Sardinia, Italy:
Results from a multicenter study**

Magrì S *et al.* Eligible features of ulcerative colitis in Italy

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Abstract

BACKGROUND

There are few data on epidemiological and clinical features of adult ulcerative colitis (UC) patients in the different Italian regions, mainly derived from the absence of a national registry. This prevents a correct interpretation of the disease burden.

AIM

To assess the main clinical and epidemiological features of adult patients diagnosed with UC in Sardinia, Italy.

METHODS

We performed a multicentre, observational, cross-sectional study including adult patients with UC, enrolled in seven Gastroenterology Unit centers in Sardinia. Data were obtained from medical patients' records and from a questionnaire administered at inclusion visit.

RESULTS

Four hundred and forty-two patients with UC were included. Median age at diagnosis was 39 years (IQR 28-48). After a median disease duration of 10 years, 53 patients experienced a proximal extension of proctitis or left-sided colitis. Seventy-five patients developed extraintestinal manifestations. Nineteen patients (4.3%) developed cancer: two colorectal cancers and 17 extra-colonic cancers. Mesalazine (5-ASA) remains mainstay of treatment for UC. Overall, 95 patients (21.5%) were exposed to one or more biologic agents, while 15 patients (3.4%) experienced a surgery, most of which colectomy.

CONCLUSION

Our results contribute to provide important insights on the clinical and epidemiological features of patients with UC and, waiting for a national Italian registry, represent eligible data of UC population in Sardinia.

Key Words: Inflammatory bowel disease-basic; Inflammatory bowel disease-clinical; Ulcerative colitis; Epidemiology; Natural history; Treatment

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Core Tip: There are few data on epidemiological and clinical features of adult ulcerative colitis patients in the different Italian regions, mainly derived from the absence of a national registry. This prevents a correct appraisal of the disease burden. A population-based observational study evaluate an entire population in defined geographic area over an extended period of time is ideal to inform natural history of disease, and also avoid selection biases associated with referral center cohort studies

INTRODUCTION

Inflammatory bowel diseases (IBD) that include Crohn's disease (CD) and ulcerative Colitis (UC), are chronic-relapsing inflammatory diseases of the gastrointestinal tract, affecting mainly the young and middle-age^[1,2].

A considerable variation in the incidence of IBD is observable around the world, as it raised quickly in western developed countries during the last 50 years of the 20th century, while the newly industrialized nations are documenting the greatest increases in incidence since the years of globalization (2000's)^[3].

Currently, in Italy, a national disease register for IBD has not been developed yet. This prevents a correct interpretation of the disease burden. Based on the disease-specific payment exemptions register, between 150000 and 200000 people are estimated to be affected by IBD, with a prevalence of 100/100000 inhabitants for MC and 121/100000 for UC. Epidemiological data from the ECCO-EpiCom inception cohort showed that the Italian incidence is 10.5/100000 inhabitants per year, indicating lower rates of new diagnosis compared to European ones ($> 25/100000$), but twofold as compared to old Italian data^[4-6].

The management of these diseases is arduous, as inflammation often persists even in the absence of gastrointestinal symptoms^[7], and this may lead to progressive bowel damage and complications requiring long-term treatments and strict medical follow-up, and in some cases hospitalizations and surgery^[8,9]. At the same time, impaired bowel function ultimately leads to a considerable burden not only for patients^[10], but also for the healthcare systems^[11].

In particular, UC affects mostly young adults around 20-40 years old with a second peak between 60-80 years, with no differences between sexes^[12,13]. Both its clinical presentation and course vary between patients and can range from mostly quiescent to chronic, refractory disease with need of surgery, sometimes being complicated by cancer or contributing to cause of death^[14].

There are few data on epidemiological and clinical features of adult UC patients in the different Italian regions, mainly derived from administrative sources such as Hospital Discharge Register^[5,15,16].

On these premises, the aim of this study was to assess the main clinical and epidemiological features of adult patients diagnosed with UC in Sardinia, including location at diagnosis, extra-intestinal manifestations, disease progression overtime, and treatment.

MATERIALS AND METHODS

Study design and population

We performed a multicentre, observational, cross-sectional study including adult patients with UC, enrolled between February 2017 and December 2018 in seven Gastroenterology/Endoscopy Units in Sardinia, an Italian region with a population of approximately 1600000 inhabitants. All patients provided written informed consent the research project has been approved by the Ethics Board (Prot. PG/2016/17911). The study was conducted according to the Helsinki Declaration.

Inclusion and exclusion criteria

We included adult patients (≥ 18 years old) with an established diagnosis of UC, based on standard clinical, endoscopic and histologic criteria.

We excluded patients < 18 years old at the time of enrollment, patients unable to understand study's questionnaires or patients previously enrolled in a randomized clinical trial.

Diagnostic Criteria

Diagnosis was made at least three months before the study inclusion and the minimum follow-up time was 1 mo. Data were obtained from medical patients' records at each centre and from a questionnaire administered at inclusion visit. Following data were collected: sex, date of birth, lifestyle (smoking habits, alcohol consumption), personal and/or familial history of neoplasia, vaccination status (hepatitis B virus [HBV], human papilloma virus [HPV] and *S. pneumoniae*), year of diagnosis and age at diagnosis, disease extent both at diagnosis and at study inclusion (according to Montreal classification)^[17], extra-intestinal manifestations (EIMs), use of UC-related medications (mesalazine [5-ASA], corticosteroids, immunosuppressors, biologic agents) and surgery. Disease extension and regression were defined as a proximal progression or distal regression from the initial extent at diagnosis, respectively, as determined by endoscopy. We also focused on elderly-onset patients, that is patients diagnosed with UC after the age of 60 years.

Statistical Analysis

Given an estimated prevalence rate of about 124 cases per 100000 inhabitants for UC in Sardinia^[16], we aimed to enroll 400 patients with UC, equivalent to 20% of UC population in Sardinia. Data were reported on Microsoft Excel worksheet and analysed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, United States). Statistics were descriptive: categorical variables were expressed as proportions, while continuous variables as median and interquartile range (IQR).

RESULTS

Sex, age at diagnosis and smoking status

Between February 2017 and December 2018, 442 patients with an established diagnosis of UC were included: 231 (52.3%) were female, with a female-to-male ratio of about 1.1 (Table 1).

Median age at diagnosis was 39 years (IQR 28-48). At the time of diagnosis, 4.5% (20/442) of patients were < 16 years old; 52.7% (233/442) were diagnosed between 17 and 40 years old and 42.8% (189/442) at age > 40. About three quarters of patients were diagnosed between 17 and 49 years old (23.2% between 17 and 29, 25.5% between 30 and 39 and 23.2% between 40 and 49).

10.9% (48/442) of patients were active smokers and 36.2% (160/442) were former smokers.

Disease extent

Disease extent at the time of diagnosis was proctitis [E1] in 81 (18.3%) patients, left-sided colitis [E2] in 178 (40.3%) and extensive colitis [E3] in 176 (39.8%). Data were not available in 7 patients (1.6%).

After a median disease duration of 10 years (IQR 3-15.5), 53 patients (12%) experienced a proximal extension of proctitis or left-sided colitis: 13 (24.5%) patients from E1 to E2, 12 (22.7%) from E1 to E3 and 28 (52.3%) from E2 to E3.

In 28 patients (6.3%) there was a regression of disease extent, after a median disease duration of 10.5 years (IQR 7-16.75): 10 patients (35.7%) from E2 to E1, 8 (28.6%) from E3 to E1 and 10 (35.7%) from E3 to E2.

EIMs, malignancies and vaccinations

Seventy-five patients (16.3%) developed EIMs, the most frequent being articular (50/72, 69.4%), followed by hepatobiliary (11/72, 15.3%, of which six patients with primary sclerosing cholangitis), cutaneous (9/72, 12.5%) and ocular (5/72, 6.9%); in three patients (4.2%) there was a combination of articular and ocular manifestations.

After UC diagnosis, 19 patients (4.3%) developed cancer: two colorectal cancers (CRC) and 17 extra-colonic cancers (five breast, four skin, two prostate, two thyroid, one pancreas, one stomach, one gastric MALT lymphoma, one multiple myeloma).

In the study population, patient self-reported vaccination rates were 30.3% (134/442) for hepatitis B virus, 2% (9/442) for human papilloma virus and 1.6% (7/442) for *S. pneumoniae*.

Medical and surgical treatment

Details on medical therapy are shown in Table 2. Twenty-eight patients (6.3%) received no UC treatment at the inclusion visit. The most common therapy at inclusion visit was 5-ASA: 368 (86.6%) of patients were taking it at baseline, while 46 (10%) withdrew it. No data were available in 17 patients. 9% of patients started with corticosteroids, either systemic or with low bioavailability, while 51.7% were exposed to one or more courses of steroids during their disease course. Azathioprine was used by 40 (9%) patients; 69 (15.6%) withdrew it during their disease course, mainly for adverse events.

Overall, 95 patients (21.5%) were exposed to one or more biologic agents: 72 patients (75.8%) were treated with one biologic agent, 17 (17.9%) with two and 6 (6.3%) with three. At study inclusion, infliximab was the most common anti-TNF α biologic used, (55/442, 12.4%), followed by adalimumab (12/442, 2.7%) and golimumab (5, 1.1%);

while vedolizumab was used in 11 (2.5%) patients. Nine of the eleven patients with VDZ were previously treated with anti-TNF α , while two were naïve to any biologic.

Eleven patients (2.5%) were treated with a combination therapy of immunosuppressant drug plus biologic, ten in association with anti-TNF α agents, one with Vedolizumab. None of the patients was treated with a combination of biologics.

A total of 15 patients (3.4%) had a resection performed. Of these, 13 patients (87%) underwent colectomy, while 2 (13%) hemicolectomy for CRC. The median time between diagnosis and surgery was 5 years (IQR 2-20). The vast majority of patient who underwent surgery were with extensive colitis at diagnosis (12 patients, 80%) compared with 3 patients (20%) with left-sided colitis.

Elderly-onset UC

Fifty-one patients (11.5%) were diagnosed with UC after the age of 60 years. Among them, 31 (60.8%) were male. Disease extent at diagnosis was E1 in 7 patients (13.7%), E2 in 24 (47.1%) and E3 in 20 (37.2%); data were not present in one patient. After a median follow-up time of 4 years (IQR 1-6), there was a proximal extension of disease in 3 patients (5.9%).

Three patients (5.9%) developed EIMs (two articular and one erythema nodosum). Four patients (7.8%) had history of neoplasia (two skin cancers, one prostate, one breast).

The most common therapy at the time of inclusion visit was 5-ASA, used by 368 (83.2%) of patients. Four patients (7.8%) were taking corticosteroids, while 50.1% received one or more courses of steroids after the diagnosis, either systemic or with low bioavailability. Two patients (3.9%) were under treatment with azathioprine, while three patients withdrew it during their disease course (two for adverse events and one for disease remission). Four patients (7.8%) were under treatment with biologic agent: three with infliximab and one with vedolizumab. No one underwent colectomy.

DISCUSSION

In this study we summarize the main characteristics and the natural history of UC in a large population study of a single Italian region, Sardinia, including demographic data, disease extension, EIMs, malignancies, vaccinations, medical and surgical treatment.

Disease extent in UC is an important feature because is an indicator of severity of disease, as well as the type of treatment needed. Patients with initially diagnosis of pancolitis appear to have a worst disease course and need a more aggressive treatment, both medical and surgical, while a distal UC is associated with better prognosis^[18]. In our cohort diagnosis of proctitis was made in 18.3% of patients, left-sided colitis in 40.3% and extensive colitis in 39.8%. The overall rate of extension was 12% after a median follow-up of 10 years, significantly lower than in others that reported highest rates^[19,20]. This feature could be explained in different ways. Firstly, a possible explanation is linked to the time of UC diagnosis that in our cohort was 39 years, substantially comparable with European data^[4], but earlier than the North American countries, where the highest rate of UC extension is reported^[21]. If the diagnosis is significantly delayed, as well as the start of therapy, patients are predisposed to a major risk of disease extension and an aggressive course. Moreover, we can speculate that Sardinia, a region geographically isolated from European continent, has a selected population, less pre-disposing to develop a more aggressive disease due to genetic or environmental factors. Among the latter, diet plays an important role in IBD pathogenesis, by modulating the gut microbiota and, consequently, it could have an impact on IBD course^[22]. In particular, if several lines of evidence point to aspects of the typical Western diet that may promote the development of IBD and its course, less is known about the beneficial role of Mediterranean diet (Md), more frequently adopted in Southern Europe, particularly in Sardinia. Md is characterized by a high intake of fruits and vegetables, olive oil and oily fish, grains and nuts^[23]. Chicco F *et al* conducted an observational study in a Sardinian population of IBD patients showing a spontaneous improvement of disease activity and inflammatory markers in patients that adopted a Md^[24]. Further prospective studies are needed in this setting.

EIMs are common in IBD and adversely impact upon patient's quality of life and some of that can be life-threatening. The real prevalence and burden of EIMs is not fully evaluated yet stands around 15%-50% since prospective studies are lacking^[25]. The analysis of clinical characteristics revealed that 16.3% of our populations experienced EIMs, the most frequent articular (69.4%), followed by hepatobiliary (15.2%), cutaneous (12.5%) and ocular (6.9%).

5-ASA remains mainstay of treatment for UC. In our cohort we observed that almost all the patients received 5-ASA, while only 10% were former used, mainly because of the concomitant treatment with immunomodulators or biologics. However more recent publications demonstrate no benefit to concomitant 5-ASA in UC patients escalated to anti-TNF α or Vedolizumab^[26]. Despite the increasing of therapeutic armamentarium available, clinics still prescribe 5-ASA even when it failed or in step-up therapy. One of the reasons could be the role of 5-ASA in CRC prevention. American guidelines suggest that 5-ASA therapy may be stopped in patients that achieved long remission or are treated with biologics^[27]. Instead ECCO guidelines emphasize the role of 5ASA in CRC prevention suggesting a withdrawal only in low-risk patients (limited disease extent, a history of remission for several years, no previous requirement of systemic corticosteroids)^[28]. Considering also the burden on healthcare budgets and the albeit rare potential adverse effects, there is the need to consider the withdrawal of 5-ASA in some subset of patients.

Regarding biological therapy we observed that 21% of patients were exposed to one or more biologic, a proportion significantly higher than the European one^[29]. This trend might follow a top-down approach with a rapid escalation as the result of the "era of mucosal healing" as a treatment goal^[30]. However, the majority of participating centers were tertiary biologic-prescribing IBD hospitals with greater propensity to use biologics. The impact of this more aggressive therapeutic approach on the disease course needs to be further evaluated. Another important finding seen in this study is that the majority of patients did not receive a combination therapy with an anti-TNF α or VDZ and an immunomodulatory drug.

Population-based cohorts of patients diagnosed after the introduction of biologics in Europe and North America have reported surgery rates of 3%-6% in UC^[13,31]. These numbers are comparable to the surgery rates observed in the present cohort. Recent studies showed a reduced rate of colectomy in UC assuming that this trend is strongly linked to use of biologic agents that positively influence the disease course^[32]. It remains to be proven if current IBD treatment strategy can influence the course in the long term.

CRC has always garnered special attention in IBD. Population-based data from our cohort demonstrate only two cases of CRC. This finding seems to be in line with the results of an Italian study conducted by *Taborelli et al*^[33], which showed that CRC risk among both UC and CD patients was similar to that expected in the general population. These data could be explained by several factors as diet, chemoprevention or colonoscopy surveillance. Differently, we observed a higher rate of extraintestinal tumors. However, it is difficult to establish whether there is an influence of the natural history of intestinal disease or is the result of unrelated factors.

Patients with IBD are vulnerable to infections because of the immunological disorder caused by the disease itself or to the immunosuppression induced by the treatment^[34]. Thus, the determination of vaccination status is important to limit under-immunization. Despite the current practice recommendations for routine vaccination in IBD^[35,36], our findings demonstrate significant deficiencies in self-reported vaccination uptake with a low rate of adherence to vaccination schedules, in particular for *S. Pneumoniae* and HPV. Inadequate counseling, deficiencies in physicians' knowledge about vaccinations and uncertainties about vaccination indications in IBD patients have been implicated as an important contributor to poor uptake of vaccination^[37]. This suggest that more attention needs to be given to vaccination counselling. A structured review of vaccination status at time of diagnosis, prior the initiation of immunosuppressive therapy and an annual review represent an optimal strategy in this setting. Contrary, in our study the rate of self-reported vaccination for HBV was 30.3%, higher than that reported in others^[38,39]. These data are clearly due to the vaccination campaign introduced in Italy in 1991 that

makes vaccination mandatory for all people born since 1979 rather than through intervention by gastroenterologists.

Our study has some limitations that need to be taken into consideration. These include the heterogeneity of the participating centers in terms of health care of which they are part. In addition, few centers have contributed to the collection of the majority of data making potentially skewed the data collection. Moreover, the study may be limited by the retrospective data collection. Although we controlled for many potential confounders, unmeasurable variables might alter data extractions.

CONCLUSION

In conclusion, not yet available a national IBD register, this is one of the first studies conducted in Italy that contributes to provide important insights on the clinical and epidemiological features of patients with UC as well as about the management and its natural history. Our data seem in line with Italian and European ones. Waiting for a national registry, our results represent eligible features of UC population in Sardinia even considering that the number of patients enrolled represents about the 20% of the population.

ARTICLE HIGHLIGHTS

Research ¹background

There are few data on epidemiological and clinical features of adult ulcerative colitis (UC) patients in Italy.

Research motivation

A population-based observational study evaluates an entire population in defined geographic area over an extended period of time. is ideal to inform natural history of disease, and also avoid selection biases associated with referral center cohort studies

Research objectives

To describe the characteristics of patients at the time of UC diagnosis, and to register the use of immunosuppressive treatments and biological drugs, surgeries and malignancies after diagnosis of UC.

Research methods

Consecutive patients with UC in ambulatory follow-up, at the time of the visit, were invited, after obtaining informed consent, to fill in a questionnaire concerning the natural history of their chronic disease object of the study.

Research results

Four hundred and forty-two patients have been included in the study. A high proportion of patients were exposed to one or more biologic. 5-ASA remains the mainstay of UC treatment. Left-sided colitis is the most frequent location.

Research conclusions

This is one of the first large-scale nationwide, observational study to investigate the epidemiological characteristics of UC in Italy. Sardinia, a region geographically isolated from European continent, could have a selected population, less pre-disposing to develop a more aggressive disease due to genetic or environmental factors.

Research perspectives

A correct and objective mapping of the epidemiological and clinical characteristics of patients with UC, but in general with inflammatory bowel disease, cannot be separated from the presence of a national register that brings together national data. It is desirable that this happens in Italy.

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