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DOTTORATO DI RICERCA IN SCIENZE BIOMEDICHE CLINICHE E SPERIMENTALI
CORSO DI DOTTORATO IN GASTROENTEROLOGIA

Direttore del corso: Prof. Dario Conte

LATE-ONSET ULCERATIVE COLITIS:

THE IG-IBD "AGED STUDY"

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease, involving the colon.

Long believed to be a disease of the young, 10-30% of patient living with inflammatory bowel disease are over the age of 60, either having aged with UC or developing it as an older adult.

The natural history of late onset ulcerative colitis, above 65 years of age, is not well defined. Disease course, response to therapy, prognosis and outcomes comparing populations with late and early onset of disease have been investigated in several studies with conflicting results [1, 2, 3, 4].

Epidemiologic studies have revealed that late onset UC, defined as onset > 60 years of age, is observed in 8 – 11% of all UC patients [1, 2, 4] thus, together with the rise of the overall incidence of UC, a sizeable number of patients can be expected to be diagnosed in the upcoming decades. No data are available from randomized clinical trials on treatment-

specific issues in elderly patients [5], namely response to therapies or safety. The available data are currently based on retrospective analyses. Based on these studies, late onset UC seems to be characterized by a milder disease course, better response to steroids [6], lower rates of disease progression, and lower need for immunomodulators (IMM) or biologics (BIO) [1, 7]. However, the less frequent use of IMM or BIO in elderly compared to younger populations may also be related to safety concerns that may limit their use by physicians and not to disease severity alone. Currently, more frequent severe infections and less favourable outcomes are reported in elderly patients treated with anti-TNF therapy [8, 9], as well as more frequent adverse events in patients on thiopurines, for example skin cancer or lymphoproliferative diseases [10, 11]. It is also well documented that elderly UC patients have more disease-related hospitalizations compared to younger patients [12, 13] and have a higher post-surgical morbidity and mortality [14, 15, 16, 17, 18].

1.1. Epidemiology

Approximately 10–15% of IBD in the USA is diagnosed after the age of 60. This incidence rate is conservative, since the true incidence of older-onset IBD can be difficult to determine due to greater difficulty in diagnosing these patients and the methodology of current epidemiological studies [3].

Older-onset UC is more common than CD, with rates higher in elderly men than women. The worldwide incidence of IBD varies by region, typically highest in Westernised nations and lowest in developing countries. The US incidence UC is 6–8/100 000/year in individuals > 60 years old. Among older patients worldwide, the incidence UC is 3–11/100 000 in Europe and 0.1–1/100 00 in Asia [1]. In Asia, approximately 15% of newly diagnosed IBD cases are > 60 years of age. When examining the largest cohort of older-onset IBD patients to date, being > 60 years old at diagnosis 1/8 of all incident UC cases. IBD incidence decreases with each subsequent

decade after age 60, with 25% of individuals being diagnosed in their 70s and 10% being diagnosed in their 80s [19].

Though the incidence and prevalence of adult IBD may be stable in several developed countries, the rates are increasing in Asia and parts of Europe among both genders and across all age groups, with the exception of the very young and those >80. The underlying reasons for this trend may be a combination of increased urbanisation, greater awareness of IBD among providers, better access to care and colonoscopy and advancements in diagnostic methods [20].

Because mortality in IBD is only very mildly elevated and the disease is most often diagnosed in the young, its overall prevalence among older individuals is expected to grow substantially [20].

1.2. Pathophysiology

Ulcerative colitis is believed to develop in genetically susceptible individuals who develop an aberrant immune system that reacts

inappropriately to gut organisms and their by-products. Environmental factors can play a role at various stages in this process but have not been specifically studied in older UC patients.

Genetics appear to be less important in older-onset UC, as opposed to patients diagnosed at an earlier age. In UC 13% of patients < 17 years old had a family history of IBD, compared with only 3% of those > 60 years old [1].

When exposed to antigens in the gut, the intestine has to distinguish innocuous from detrimental antigens. This distinction is aided by an intact and functional intestinal epithelium, the innate immune system and an adaptive immune system, consisting of primarily B and T cells, which respond to foreign antigens. In ageing, a reduction in the number of naive T cell precursors and an impaired ability of virtual memory T cells contribute to reduced T cell responses [21].

This age-related immunosenescence is associated with changes in intestinal microbiota composition, increasing the risk of an aberrant immune

system and development of IBD.

The effect of ageing on the human gut microbiota and its balance with the host's immune system, may be related to the progression of geriatric syndromes and diseases in the elderly population. Major physiological changes impact on the composition and function of the intestinal microbiota in older adults, including decreased intestinal motility, prolonged transit time, faecal retention, nutritional changes associated with decreased sense of smell and taste, dental decay, and dysphagia. Furthermore, the increased use of medications including laxatives and antibiotics also affects the gut microbiota.

The composition of bacteria changes in the elderly, with a decrease in anaerobes [e.g. *Bifidobacteria*], in both abundance and species diversity and an increase in facultative anaerobes, including streptococci, staphylococci, enterococci, and enterobacteria, a balance that is associated with IBD. Moreover, a geriatric syndrome characterised by restricted physiological reserves and an impaired resistance to stressors, may be

associated with a more profound gut dysbiosis. *Van Tongeren et al.* found that frail elderly have up to 26-fold less anaerobes and -fold more enterobacteria than healthy or less frail elderly [21].

1.3. Differenzial diagnosis & clinical presentation

Establishing a definitive diagnosis of UC in older adults can be challenging. Illness in older adults is often complicated by the physical changes of ageing, associated comorbidities and atypical presentations. The unreliability of physical examination findings and lack of sensitivity of laboratory testing are commonly encountered and further complicate the diagnostic process. In addition, even with advancements in diagnostic tools, intestinal inflammation from various causes can mimic UC [**Table 1**] [21]. The clinical presentation of UC upon diagnosis differs between older and younger patients [**Table 2**]. When compared with younger patients, older-onset UC more frequently presented with isolated colonic inflammation,

patients tend to have less isolated proctitis, but more left colon inflammation and present with less rectal bleeding and abdominal pain [21].

Disease	Clinical characteristics	Distinguishing findings
Infectious colitis	Diarrhoea (with possible blood), fever	Positive stool studies, Pseudomembranes on endoscopy (*Clostridium difficile* infection)
NSAID-induced enterocolitis	Diarrhoea (with possible blood), iron deficiency anaemia, obstruction, perforation	Diaphragm-like small bowel stricture, elderly especially at risk
Ischaemic colitis	Acute onset of abdominal pain, followed by bloody diarrhoea	Segmental area of injury, rectal sparing, abrupt transition between normal and affected mucosa
Segmental colitis associated with diverticula [SCAD]	Bloody stools diarrhoea, abdominal pain	Inflammation only in and around diverticulum
Radiation colitis	Bloody diarrhoea, urgency, tenesmus occur weeks to years after abdominal/pelvic radiation	Histologically: fibrosis and capillary telengiectasia
Diversion colitis	Occurs in surgically diverted bowel loop, most asymptomatic, but can have abdominal pain and bloody/mucous discharge	Histologically: prominent lymphoid hyperplasia
Solitary rectal ulcer syndrome	Rectal bleeding, straining, pelvic fullness	Histologically, thickened mucosal layer and crypt architectural distortion, smooth muscle and collagen replace lamina propria

Table 1. Differential diagnosis of ulcerative colitis in the elderly [21].

Overall, at diagnosis, older-onset UC may be associated with fewer signs and symptoms, with the pattern most likely related to the location of disease

and the decreased intestinal inflammatory burden [21].

Clinical manifestation	Elderly	Younger adults
Overall symptoms	More subtle	More flagrant
UC symptoms	Less abdominal pain and rectal bleeding	More abdominal pain and rectal bleeding
Disease location	More left-side colonic inflammation, less isolated proctitis	More extensive colitis
Disease course	Localization of disease more lickely to remain stable	Localization of disease more lickely to extend
Extra-intestinal manifestations	Less common	More common

Table 2. Clinical manifestations of UC in elderly versus younger adults [21].

1.4. Treatment

The approach to UC treatment includes three main goals:

1] induce and maintain remission;

2] prevent disease-related complications;

3] improve quality of life and minimise adverse events.

Treatment strategies are based on the location and severity of inflammation and take into consideration the perceived natural history of the

disease [21].

Older-onset UC typically is not associated with disease progression [**Table 2**]. In a French cohort with follow-up over at least 2 years, only 3% of UC patients with proctitis and 5% of UC patients with left-sided colitis, progressed to extensive colitis. Overall, the extent of UC remained stable in 84% of patients. Over time, 0–17% of patients > 60 years old have progression of their disease, at rates lower than those seen in younger patients [1].

Determining the most appropriate therapeutic approach in the elderly is challenging due to multiple factors. First, there is a lack of drug efficacy trials in older patients, as most are excluded, particularly from trials with immunosuppressive agents. Also, appropriate clinical endpoints are unclear in the elderly. Additionally, multimorbidity increases the complexity of medical therapy decisions and polypharmacy elevates the risk of non-compliance and drug interactions [22].

2. METHODS

2.1. Aim of the study

The aim of the **A**ssessment of IBD in **G**eriatric patients and **E**volution of **D**isease (AGED)- study was to assess the differences in disease severity and extension at UC onset in three different age groups and to compare the disease course and patterns in the following 3 years from diagnosis.

2.2. Study design

The AGED-study is a retrospective multicentre study conducted by the Italian Group for the study of IBD (IG-IBD) in 20 referral centres across Italy. Consecutive subjects diagnosed with UC between 2005 and 2010 according to established endoscopic and histological criteria [23], with disease onset at the age of 65 years or above (target group, elderly) were included. For each patient of the target group, one consecutive patient diagnosed with UC between age 40 and 64 years (adults), matched for sex, and two additional sex-matched patients diagnosed before age 40 years (young patients) in the same study period were

included. To analyse the disease characteristics at onset and first-line treatment, all data concerning diagnosis, clinical and endoscopic activity, medications and surgery had to be available in each centre database for the first year. To analyse the disease course according to patterns, the need for any treatment or surgery and data on response to therapy in the follow-up period, only the data from regularly assessed patients (at least two visits in the follow-up period) were included for a global follow-up time of 3 years from diagnosis. Subjects with undefined IBD or Crohn's disease or microscopic colitis were also excluded.

The following data were collected: time to diagnosis, defined as interval between symptom onset and definite diagnosis, smoking status (current, former, and ex-smokers), haemoglobin and C-reactive protein (CRP) levels at diagnosis, extension of disease at diagnosis according to the Montreal classification [24] and severity of disease according to the endoscopic Mayo subscore [25] at onset and during the follow-up. In addition, data on previous and/or concomitant extraintestinal manifestations (EIM) and concomitant diseases, expressed as the Charlson Comorbidity Index (CCI) [26], were collected. In the follow-up period,

therapy with mesalazine (5-ASA), steroids (systemic steroids or low bioavailability steroids; l.b.s.), IMM therapy (thiopurines or methotrexate), anti-TNFs (BIO) and surgery rates were reviewed. Response to steroids in the first year was defined as no further prescription of steroids, or therapy with IMM, BIO, or surgery in the subsequent 12 months, after the first course of steroids. Response to IMM was defined as no further prescription of steroids, BIO or UC-related surgery after start of therapy with IMM or no discontinuation of IMM due to side effects. Moreover, the study population was stratified according to disease pattern at the end of the observation period as follows:

Pattern 1) disease onset and subsequent mild or no activity

Pattern 2) relapsing behaviour (more than one flare/year with remission time > 3 months)

Pattern 3) chronically active disease defined as no remission lasting more than 3 months.

Assessment of the disease patterns was performed according to Henriksen [27], excluding patients colectomized within the first year or patients lost to

follow-up after the first year. Data concerning the onset of UC and response to steroids were analyzed and compared among the 3 study groups, whereas the follow-up data over 3 years were analyzed by disease pattern and compared between pattern 1 and pooled patterns 2 and 3.

Parameters with more than 5% data lacking were excluded from analysis.

The study design was approved by the IG-IBD scientific committee and, subsequently, approved by the local ethics committee of the coordinating centre (Messina, Protocol n. 02/2013; February 25th, 2013). All data were collected and handled anonymously according to the national law on data protection.

2.3. Data presentation and statistics

Numerical data were expressed as means ± standard deviation (SD), medians [min-max] or proportions (%) as appropriate. The chi square test, Fisher's Exact test or the Log-likelihood Ratio were used to compare categorical variables. Continuous variables were compared using the Kruskal-Wallis H test with the Dunn's test for multiple comparisons.

Logistic regression models (univariate and multivariate) were constructed to identify significant risk factors for the need for immunosuppression or to undergo colectomy.

To compare the cumulative risk of treatment with immunomodulators or biologics and to be colectomized between the three groups in patients with pattern 1 or with pattern 2-3, a Kaplan-Meier survival estimate was sought, accompanied by the log rank test of equality over strata.

All comparisons utilized a two-sided significance level of 0.05. Data analysis was carried out with SPSS Statistics for Windows, version 17.0, Chicago: SPSS Inc.

A p value <0.05 was considered statistically significant.

3. RESULTS

A total of 1091 patients distributed in the three age groups were included in the final analysis. Demographic data and baseline characteristics are summarized in **Table 3 a-b**. Median time to diagnosis was significantly longer in young patients compared to adults ($p<0.0001$), but not different compared to the elderly. Former smokers were more prevalent ($p<0.0001$) in adults and in elderly. Conversely, never smokers were more prevalent ($p<0.002$) in young patients than in the other two groups. No difference was found for current smokers. The CCI was significantly higher in the elderly and adults compared to younger patients ($p<0.0001$). Diabetes (24%, 15%, and 1%, respectively in the elderly, adults, and young patients), heart disease (myocardial infarction, congestive heart failure; in 15%, 6%, and 0.5%), lung disease (obstructive lung disease, asthma; in 12%, 7%, and 0.6%), chronic kidney disease (in 6%, 4%, and 0.2%), neuro-psychiatric disorders (in 5%, 1%, and 0.2%), and chronic liver diseases (mostly HCV-related diseases; in 0.7%, 3%, and 0.8%) were the most common comorbidities observed in the study population.

	elderly ≥65 yrs n=283	**adults** 40-64 yrs n=285	**young patients** <40 yrs n=523	p-value
Age at diagnosis (years)	71.4 ± 5.6	55.2 ± 9.4	26.9 ± 8.5	-
Male	161 (56%)	187 (66%)	280 (54%)	-
Time to diagnosis (months)	1 [0-96]	0 [0-48]	2 [0-168]	<0.0001
Haemoglobin at diagnosis (g/dl)	11.7 ± 1.9	12.2 ± 1.9	12.3 ± 1.9	0.174
Smoking habits; n (%)				
active	18 (6.8%)	19 (7.0%)	56 (10.9%)	0.063
ex-smokers	95 (35.7%)	102 (37.4%)	82 (16.0%)	<0.0001
never smokers	153 (57.5%)	152 (55.6%)	375 (73.1%)	<0.0001
Charlson comorbidity index				
CCI 0, n(%)	187 (66.8%)	217 (75.3%)	505 (96.6%)	<0.0001
CCI 1, n(%)	65 (23.2%)	59 (20.5%)	18 (3.4%)	<0.0001
CCI 2, n(%)	26 (9.3%)	11 (3.9%)	0 (0%)	<0.0001
CCI 3+, n(%)	2 (0.7%)	1 (0.3%)	0 (0%)	<0.0001
Extraintestinal manifestations; n (%)	16 (5.7%)	13 (4.6%)	23 (4.4%)	-
Bone and joint	7 (2.5%)	10 (3.5%)	7 (1.3%)	0.555
Skin	5 (1.8%)	2 (0.7%)	3 (0.6%)	0.021
Liver	0 (0%)	0 (0%)	7 (1.3%)	0.004
Eye	2 (0.7%)	1 (0.3%)	3 (0.6%)	0.964
Other	2 (0.7%)	0 (0%)	3 (0.6%)	0.082

Table 3 a. General and clinical data of the three patient groups at diagnosis.

Medians [min-max], means±SD and proportions (%) are presented as appropriate.

Extraintestinal manifestations of IBD at maximal follow-up: bone and join includes osteopenia, osteoporosis and spondylarthropthies; skin includes pyoderma gangrenosum, erythema nodosum and psoriasis; liver includes primary biliary cirrhosis and primary sclerosing cholangitis; eye includes uveitis and episcleritis; other includes thrombosis and vasculitis.

	elderly ≥65 yrs n=283	**adults** 40-64 yrs n=285	**young patients** <40 yrs n=523	p-value
Montreal, n(%)				0.185
E1	36 (12.7%)	32 (11.6%)	60 (11.5%)	
E2	158 (55.8%)	172 (60.7 %)	272 (52.0%)	
E3	89 (31.5%)	81 (28.8 %)	191 (36.5%)	
Disease severity, n(%)				<0.0001
Mayo 1	75 (26.5%)	90 (31.6%)	87 (16.6%)	
Mayo 2	146 (51.6%)	160 (56.1%)	338 (64.6 %)	
Mayo 3	62 (21.9%)	35 (12.3%)	98 (18.8 %)	

Table 3 b. Disease extension according to the Montreal classification and disease severity according to the endoscopic Mayo subscore at diagnosis in the three study groups.

Although not included in CCI calculation, hypertension was the most frequent disease found in 43%, 29%, and 2% of patients [**Figure 1**].

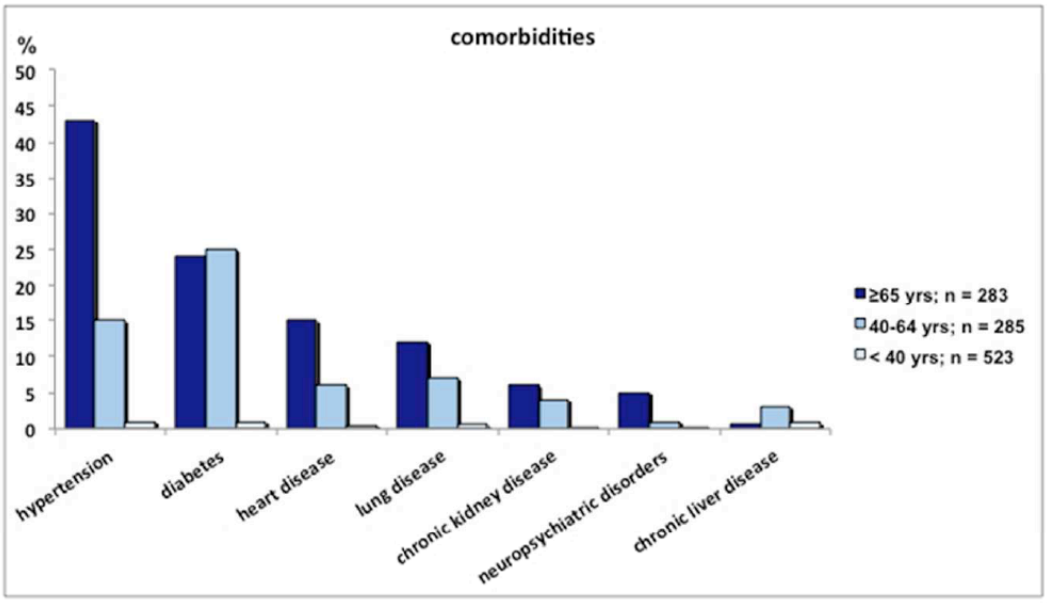

Figure 1. Prevalence of comorbidities in the 3 age groups.

Before diagnosis of UC, extraintestinal manifestations (EIM) were similar in the 3 groups (3.2% in the elderly, 3.8% in adults, and 3.3% in young patients) increasing to 5.7%, 4.6% and 4.4% at 3 years, respectively. The frequency of liver disease differed between the three gropus (p 0.0004). In particular, young patients showed a higher number of hepatic EIM, such as primary biliary cirrhosis (1/523) and primary sclerosing cholangitis (6/523), compared to the elderly and adults. Skin related EIM were more frequent in the elderly (p=0.021).

3.1. Extension and severity of UC at diagnosis.

Extension of disease according to the Montreal classification at the moment of diagnosis was similar in the 3 groups [**Table 3 b**]. Conversely, endoscopic activity at diagnosis differed between the 3 groups (p<0.0001). Mild activity was significantly more frequent in the elderly and adults than in young subjects.

Moderate disease activity (Mayo 2) was the most frequent presentation of disease in all age groups (from 51.0% to 64.6%), but was significantly more prevalent in young patients than in the elderly. Severe disease at onset was less frequent in adults compared with the elderly.

3.2. Disease pattern

The relative distribution of disease patterns is given in **Figure 2**.

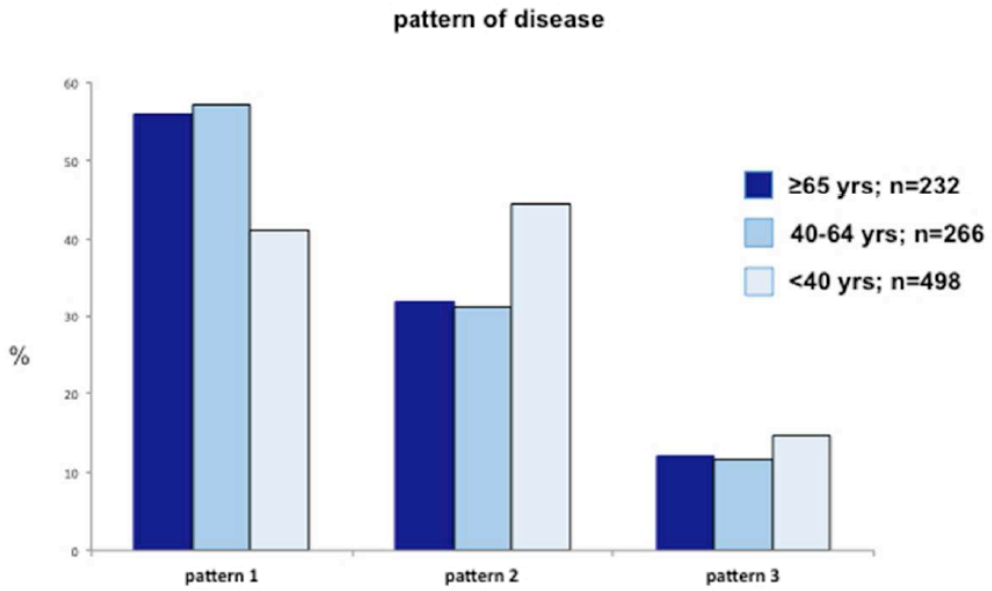

Figure 2. Distribution of disease patterns in UC diagnosed ≥65 yrs (n=232; elderly), between 40-64 yrs (n=266; adults), and subjects diagnosed <40 yrs (n=498; young patients) (p=0.00002); pattern 1 is characterized by disease onset and subsequent decline of activity, pattern 2 by chronic relapsing disease, and pattern 3 by chronic active disease.

Disease pattern were significantly different in the 3 groups (p 0.00002). In particular, pattern 1 was more frequently observed in the elderly (56.0%) and adults (57.1%) compared to young patients (41.0%) ($p<0.0001$ for both comparisons). Pattern 2 was more frequent in the younger patients (44.4%) compared to the elderly ($p<0.002$) and adults ($p<0.0001$) (31.9% and 31.2%, respectively), whereas pattern 3 was equally distributed in the 3 groups (elderly: 12.2%, adults: 11.7%, young subjects: 14.7%; p 0.458).

3.3. Therapy at diagnosis and at follow-up

Therapies at diagnosis and the need for different drug classes thereafter are shown in **Table 4.** Data are analyzed comparing pattern 1 vs. pooled pattern 2-3.

	Pattern 1				Pattern 2-3			
	elderly ≥65 yrs	**adults** 40-64 yrs	**young patients** <40 yrs	**p-value**	**elderly** ≥65 yrs	**adults** 40-64 yrs	**young patients** <40 yrs	**p-value**
1 st year; n (%)	**n=130**	**n=152**	**n=204**		**n=102**	**n=114**	**n=294**	
5-ASA	129 (99.2)	149 (98.0)	202 (99.0)	0.619	96 (94.1)	110 (96.5)	289 (98.3)	0.091
Systemic steroids	55 (42.3)	47 (30.9)	92 (45.1)	0.021	59 (57.8)	57 (50.0)	184 (62.6)	0.066
IMM	9 (6.9)	8 (5.3)	22 (10.8)	0.143	14 (13.7)	16 (14.0)	43 (14.6)	0.971
BIO	1 (0.8)	0	1 (0.5)	0.587	8 (7.8)	3 (2.6)	11 (3.7)	0.129
2nd year; n (%)	**n=130**	**n=152**	**n=204**		**n=102**	**n=114**	**n=294**	
5-ASA	118 (90.8)	139 (91.4)	190 (93.1)	0.709	92 (90.2)	106 (93.0)	281 (95.6)	0.131
Systemic steroids	21 (16.2)	16 (10.5)	31 (15.2)	0.322	51 (50.0)	43 (37.7)	139 (47.3)	0.137
IMM	8 (6.2)	10 (6.6)	31 (15.2)	0.006	20 (19.6)	23 (20.2)	89 (30.3)	0.030
BIO	1 (0.8)	0	4 (2.0)	0.217	6 (5.9)	6 (5.3)	43 (10.5)	0.133
3rd year; n (%)	**n=120**	**n=144**	**n=193**		**n=87**	**n=110**	**n=279**	
5-ASA	98 (81.7)	134 (93.1)	176 (91.2)	0.006	71 (80.5)	101 (91.8)	256 (91.8)	0.007
Systemic steroids	10 (8.3)	12 (8.4)	12 (6.2)	0.689	36 (41.4)	35 (31.8)	114 (40.9)	0.223
IMM	6 (5.0)	12 (8.3)	26 (13.5)	0.034	18 (20.7)	27 (24.5)	102 (36.6)	0.005
BIO	0	0	3 (1.6)	0.074	5 (5.7)	4 (3.6)	44 (15.8)	0.001
time-to-first IMM months; median [min-max]	9,5 [4-22]	5 [1-35]	10,5 [1-29]	0.431	11 [4-24]	5,5 [1-22]	16 [1-36]	0.317
time-to-first BIO months; median [min-max]	6 [4-40]	0	15 [7-23]	0.285	9,5 [2-32]	12,5 [5-29]	21,5 [7-34]	0.687
Surgery; n (%) Years 2- 3	2 (1.5)	0	0	0.071	8 (7.8)	5 (7.6)	16 (5.4)	0.528

Tab. 4: therapy according to disease pattern in the first 3 years from diagnosis. 5-ASA = mesalazine; IMM=immunomodulators; BIO= biologics.

3.3.1. 5-ASA

In the first two years from diagnosis, 5-ASA was prescribed equally in both pattern groups; only in the third year was 5-ASA significantly less frequently employed in the elderly, regardless of disease pattern.

3.3.2 Steroids

The use of systemic steroids was similar within the two pattern groups, except for pattern 1 in the first year (p 0.021), where a lesser steroid use was observed in adults. In patients with pattern 2-3, except for the first year from diagnosis, steroids were used 3 to 6-fold more frequently than in patient with pattern 1. The use of l.b.s was not statistically different in any year between the two pattern groups (data not shown).

Response to systemic steroids after a first course is shown in **Figure 3**. The overall analysis of the three groups, irrespective of disease pattern showed similar remission rates across the groups, ranging from 32% to 45% at year 1

from diagnosis, and from 25% to 32% through year 2. No statistical differences were found.

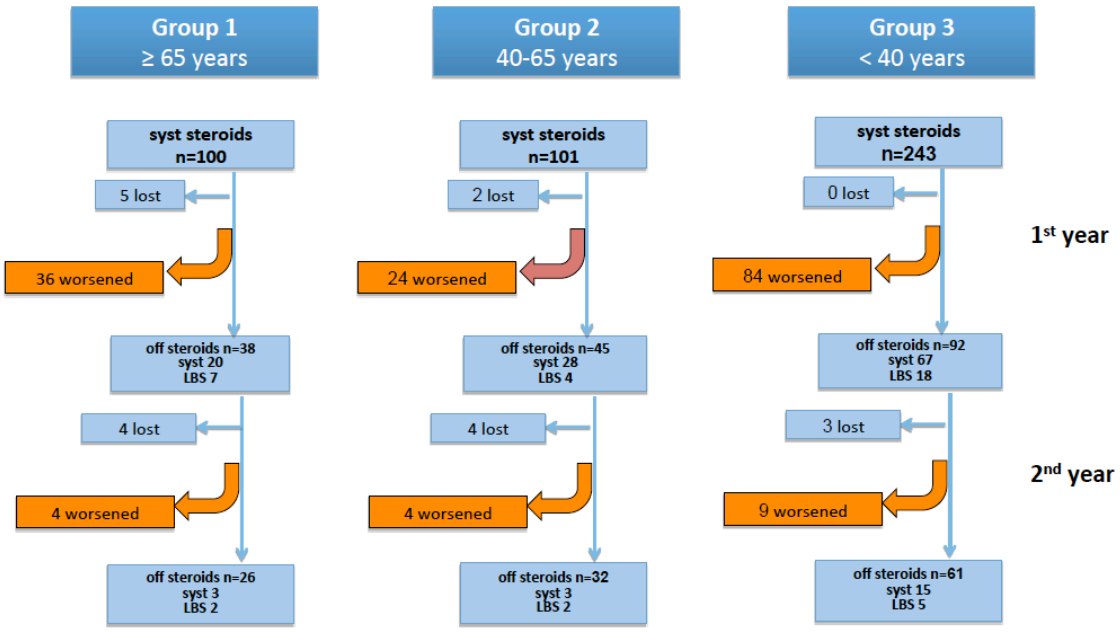

Figure 3. response to systemic steroids in the 3 study groups; syst.= systemic; LBS=low bioavailability steroids; worsening disease is defined by the need for IMM, BIO, or colectomy.

3.3.3. Immunomodulators

Out of 286 subjects receiving IMM during the study period, 253 (89%), received azathioprine, 29 subjects received 6-mercaptopurine (10%), and 5 were treated with methotrexate (1%) and, for statistical analysis, the treatments were pooled.

The analysis, stratified by disease pattern showed no differences for IMM prescription in the first year after diagnosis. Two and 3 years after diagnosis, in patient with pattern 1 and those with pattern 2-3, a significant lesser use of IMM was observed in the elderly and adults compared to young patients. Moreover, the Kaplan-Meier curve analysis (**Figure 4 A-B**) confirmed that IMM were statistically significantly underused in the elderly and adults in both disease patterns. (pattern 1, p 0.0041; pattern 2-3, p 0.0034).

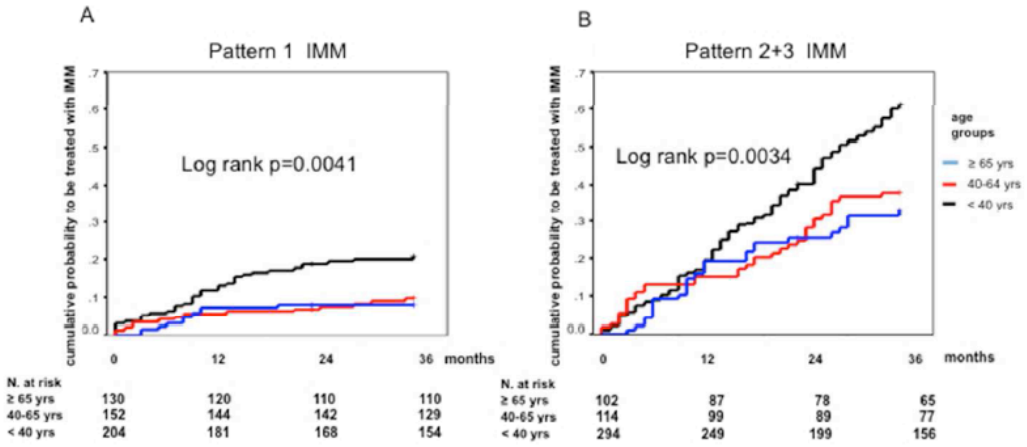

Figure 4. Cumulative risk to be treated with IMM in UC patients with disease pattern 1 (A) and with disease pattern 2-3 (B).

No differences were observed in terms of time-to-first IMM (**Table 4**). Treatment success was similar in the 3 groups (44.4% of patients in the elderly, 36.7% in adults and 50% in younger patients).

3.3.4. Biologics

All data refer to Infliximab, which was the only monoclonal antibody licensed for UC in Italy during the study period (adalimumab was used in 2 patients as compassionate use for intolerance or no response to infliximab). In UC with pattern 1, BIO were equally prescribed in 2% of patients. In patients with combined pattern 2-3, BIO were more frequently prescribed in younger patients during the third year compared to the elderly and adults (p 0.005). Of note, during the third year, BIO prescription was 3-fold higher in younger subjects than in patients>40 years. There was no difference in median time-to-first prescription of BIO between the groups.

3.4. Predictive factors for immunosuppression

3.4.1. Risk factors for IMM treatment

Univariate analysis (**Table 5**) showed that disease pattern 2-3, pancolitis, a more severe disease at onset and steroid use in the first year after diagnosis, were significantly associated to the use of IMM during the study period; whereas

higher age at diagnosis, higher CCI, chronic renal failure and multiple concomitant medications for comorbidities, were associated with lower use of IMM.

	Univariate			Multivariate		
Variable	**OR**	**95%CI**	**p<value**	**OR**	**95%CI**	**p<value**
Extensive disease	1.994	1.592-2.499	0.0001	1.539	1.179-2.009	0.007
Severe disease	1.275	1.024-1.588	0.030	-		
Pattern 2-3	4.294	3.138-5.876	<0.0001	3.724	2.647-5.238	0.0001
Steroids in the first year	5.095	3.731-6.956	<0.0001	3.592	2.553-5.054	0.0001
Higher age at diagnosis	0.977	0.970-0.984	<0.0001	0.979	0.963-0.994	0.007
Charlson comorbidity index	0.779	0.719-0.843	<0.0001	-		
Chronic renal failure	0.209	0.049-0.886	0.03	-		
Multiple co-medications	0.864	0.759-0.982	0.025	1.234	1.001-1.520	0.049

Table 5. Risk factors for treatment with immunomodulators.

On multivariate analysis, only steroid use in the first year, disease pattern 2-3, pancolitis at diagnosis, multiple concomitant medications and younger age at diagnosis were associated to IMM use.

3.4.2. Risk factors for BIO treatment

Disease pattern 2-3, use of steroids in the first year after diagnosis, use of IMM within the first year were significantly associated to the prescription of BIO

at univariate analysis (**Table 6**), whereas older age at diagnosis, higher CCI and co-medications, for concomitant diseases, were associated with lower prescription.

	Univariate			Multivariate		
Variable	**OR**	**95%CI**	**p<value**	**OR**	**95%CI**	**p<value**
Pattern 2-3	14.973	6.471-34.649	<0.0001	10.791	4.603-25.294	<0.0001
Steroids in the first year	8.650	4.558-16.416	<0.0001	4.553	2.314-8.958	<0.0001
IMM in the first y	4.292	2.667-6.907	0.001	2.715	1.551-4.751	<0.0001
Higher age at diagnosis	0.978	0.967-0.989	<0.0001	-		
Charlson comorbidity index	0.717	0.625-0.824	<0.0001	0.649	0.458-0.919	0.015
Multiple co-medications	0.742	0.579-0.950	0.018	-		

Table 6. Risk factors for treatment with BIO; IMM= immunomodulators

On multivariate analysis only disease pattern 2-3, steroids or IMM used in the first year and a lower CCI were confirmed to be associated to BIO use.

3.4.3. Need for colectomy

Through the first 3 years from diagnosis, 58/1091 patients (5.3%) underwent colectomy. Main indications were: refractory disease, fulminant disease and dysplasia or colon cancer (the latter only in the elderly and adults).

There was no difference between the three groups overall, but when analysed for disease patterns, every age group was more frequently operated on when presenting pattern 2-3 (p 0.016) (significance not included in table 4).

3.4.4. Risk factors for surgery

Patients with pattern 2-3, pancolitis, need for steroids, IMM or BIO in the first year from diagnosis were more likely to undergo colectomy through the follow-up period (**Table 7**); no protective factor was identified and all these parameters, except the use of IMM, were confirmed on multivariate analysis as a risk factor for colectomy.

	Univariate			**Multivariate**		
Variable	**OR**	**95%CI**	**p<value**	**OR**	**95%CI**	**p<value**
Pattern 2-3	5.893	2.753-12.615	<0.0001	3.961	1.810-8.667	0. 001
Extensive disease	2.121	1.347-3.338	0.001	1.685	1.028-2.760	0.038
Steroids in the first year	4.008	2.099-7.654	<0.0001	2.195	1.067-4.514	0.033
IMM in the first year	3.310	1.821-6.017	<0.0001	-		
BIO in the first year	12.571	5.830-27.106	<0.0001	5.932	2.528-13.922	<0.0001

Table 7. Risk factors for colectomy; IMM= immunomodulators; BIO= biologics

3.4.5. Diagnosis of malignancies in follow-up

Malignancies occurring through the study period were stratified into three categories:

1. colorectal cancer (CRC), including adenomas with high-grade dysplasia,

2. extracolonic epithelial tumours,

3. haemopoetic tumours.

No differences in rates of malignancies were found in the 3 study groups, except for CRC, which was more frequent in the elderly (p 0.004).

Exposure to IMM and BIO was not associated with malignancies in the 3 study groups and this was confirmed at uni- and multivariate analysis. Advanced age at UC diagnosis (OR 1.026, 95%CI 1.006-1.047, p 0.012), concomitant diabetes (OR 3.228, 95%CI 1.327-7.852, p 0.01), concomitant chronic pulmonary disease (OR 3.538, 95%CI 1.176-10.643, p 0.025) and steroid use in the first year after diagnosis (OR 2.33, 95%CI 1.007-5.55, p 0.048) were found to be risk factors for malignancies at univariate analysis.

On multivariate analysis, advanced age at UC diagnosis remained the only risk factor significantly associated with malignancies (OR 1.022, 95%CI 1.001-1.044, p 0.044).

3.4.6. Deaths

In the overall population, deaths occurred in 12/283 of the elderly (4%), 12/285 (4%) of adults and 2/523 of younger patients (0.4%, p<0.0001). On univariate analysis, age ≥ 65 years (OR 1.064, 95%CI 1.035-1.095, p<0.0001), concomitant diseases (OR 1.836, 95%CI 1.429-2.361, p<0.0001), diabetes (OR 3.983, 95%CI 1.691-9.382, p 0.002), pulmonary disease (OR 3.510, 95%CI 1.167-10.559, p 0.025) and multiple co-medications for concomitant diseases (OR 1.401, 95%CI 1.117-1.757, p 0.003) were significantly associated with death. On multivariate analysis, age ≥ 65 years at UC diagnosis remained the only risk factor (OR 1.059, 95%CI 1.029-1.089, p<0.0001).

4. DISCUSSION

Disease course is usually thought to be milder in late-onset UC. Previous data show that only a minority of elderly patients require IMM for disease control [1, 28, 29]. In our large, multicenter Italian cohort, we showed for the first time that the disease pattern determined the need for more aggressive therapies and surgery also in late-onset UC patients, without clinically important differences compared to younger age groups. We limited the observation time from 2005 to 2014 in order to include the period after the license of the first approved anti-TNF for UC in Italy (infliximab). Of note, although mild severity was the most frequent pattern of disease in late-onset UC patients, up to 44% presented with a behaviour which was not controlled by therapy. Moderate disease activity was the most frequent presentation at diagnosis in all groups, irrespective of the subsequent pattern of disease, as well as age at onset. Our study did not confirm a more aggressive onset compared to young patients, followed by prolonged remission in elderly UC patients as previously shown [30, 31], nor differences for response to steroids or IMM compared with younger age groups [6]. When the

entire cohort was analysed for steroids use, irrespective of disease pattern, we found that less than 50% of the elderly required steroids in the first year, decreasing to 20% in follow-up. This was consistent with the French cohort [1]. Interestingly, when we stratified the elderly population by disease patterns, the use of steroids was significantly higher in patterns 2-3, ranging from 60% in the first year to 40% in the third year. Despite disease pattern 2-3, we found that IMM were significantly less used in the elderly and adults than in younger patients, suggesting an undertreatment with IMM in such populations. This is confirmed by the univariate and multivariate analyses, which show that patients with disease patterns 2-3, requiring steroids in the first year, are more likely to receive IMM, but older age and concomitant disease that require multiple medications are the main limitation for their prescription. Similar data were found for the use of BIO. Our data reveal that safety concerns associated to older age would limit the use of effective medications in late-onset UC, rather than a milder course.

We found that disease extension at onset was different from previous reports. In our cohort, the minority of patients (12%) presented with proctitis,

without age differences, compared to more than 30% in previous studies [1, 28, 29]. Unfortunately, we could not assess the rate of disease progression in terms of colonic involvement over time.

The overall need for surgery was lower than reported in literature [29, 32], since only 5% of the entire study population required colectomy through year 3, which was consistent with the results from a large Canadian cohort [32]. Major risk factors were represented by disease pattern 2-3 and extensive disease, together with the need for steroids and BIO in the first year, in line with former reports [1, 31], while age was not associated to different surgery rates, as also reported by *Lakatos et al* [28].

Higher CCI was observed in the elderly, as expected, with figures roughly comparable with those reported by *Ananthakrishnan et al* [12]. Of note, our elderly cohort was much healthier than the one reported by *Juneja et al.* [26], probably due to different lifestyle factors and healthcare systems in Italy and in the US.

The occurrence of CRC was more frequent in the elderly, despite a shorter disease duration compared to high-risk populations usually requiring surveillance program [34], although a recent population-based study showed that CRC occurred earlier (median time 17 months) in late-onset UC [35].

The crude mortality rate in our cohort was 4.2% in the elderly, which is consistent with the IBSEN cohort [36]; most deaths were unrelated to UC in the elderly, but related to comorbidities and advanced age, whereas one fatality related to UC (sepsis after colectomy) was observed in a young patients.

To our knowledge, this is the first large cohort study analyzing late-onset UC according to disease pattern. We found for the first time that late-onset UC patients presenting with patterns 2-3 are frequently undertreated most likely because of medical concerns. The limitations of this study derive mainly from the retrospective study design and lack of long-term follow-up.

5. CONCLUSION

In conclusion, almost half of late-onset UC patients present an aggressive course, which is frequently undertreated. Therapeutic decisions regarding the elderly seem to be influenced by comorbidities and concomitant medications more than by disease severity. More studies on the therapeutic management of late-onset UC balancing clinical outcomes and safety concerns are needed in this particular setting.

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