Original Research

GASTROENTEROLOGY

Young age and short duration of the disease are associated with more frequent relapses in inflammatory bowel disease patients

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Abstract

Aims. To evaluate the effects of the clinical predictors such as age, duration of disease, sex, and smoking on the frequency of relapses in IBD patients.

Methods. This study recruited 289 IBD (133 with CD and 156 with UC) patients. All were followed-up for 36 months for relapses of the disease. We defined as frequently relapsing (≥1/year) patients with at least one relapse per year and as infrequently relapsing those with less than one relapse per year (<1/year). We assessed the effect of the clinical predictors: age, duration of disease, sex, and smoking on the frequency of relapses in IBD patients.

Results. Sixty-four (48.1%) of the CD patients were frequently relapsing and 69 (51.9%) were infrequently relapsing. There was a significant association between the age and the frequency of relapse (p=0.001; OR 0.964; 95% CI 0.941-0.987, p=0.002) and between the duration of the disease and frequency of relapse (p<0.001; OR 0.740, 95% CI 0.655-0.837, p<0.001). Seventy-two (46.2%) of the UC patients were frequently relapsing and 84 (53.8%) were infrequently relapsing. There was a significant association between the age and the frequency of relapse (p=0.001; OR 0.964, 95% CI 0.941-0.987, p=0.002) and between the duration of the disease and frequency of relapse (p<0.001; OR 0.740, 95% CI 0.655-0.837, p<0.001).

Conclusion. We demonstrate in a relatively significant cohort of IBD patients that young age and short duration of the disease are associated with more frequent relapses.

Keywords: Crohn's disease, ulcerative colitis, relapses, clinical predictor

Introduction

Inflammatory bowel disease (IBD) is characterized by a relapsing and remitting course. The aim of therapy is both to induce and maintain an enduring remission and to avoid disease progression and future complications. Disease flares occur randomly and are mostly unpredictable, and persistent inflammatory activity negatively affects the patient's everyday well-being, social performance, working capacity, and quality of life [1].

Despite an effective medical therapy that could lead to clinical remission, a degree of subclinical inflammation may persist within the mucosa of the gut, contributing to a risk of "symptomatic" relapse, which occurs when the inflammatory process reaches a critical intensity [2]. Identifying objective markers able to reveal such subclinical inflammation could represent a significant advance in clinical practice, allowing the gastroenterologist to select patients and plan a tailored treat-to-target treatment.

Clinical predictors of IBD recurrence have probably been the most widely studied, and they are easy to be used in everyday clinical practice [3-5]. The risk of over-treating patients could be reduced in theory with the use of

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clinical factors present at diagnosis and able to predict the subsequent course of IBD.

In the current study, we aimed to evaluate the effect of the clinical predictors age, duration of disease, sex, and smoking on the frequency of relapses in IBD patients.

Patients and methods

This prospective observational study recruited 289 IBD (133 with CD and 156 with UC) patients referred to the IBD outpatient clinic of "Tsaritsa Yoanna" University Hospital in Sofia between March 2014 and February 2018. Only patients fulfilling all inclusion and exclusion criteria were enrolled. As inclusion criteria, we used: age 18–85 years, known CD or UC diagnosed according to the ECCO Guidelines [6,7] and completion of written informed consent. The exclusion criteria were as follows: colorectal cancer or colon polyps, indeterminate colitis, history of colorectal surgery, pregnancy, history of active non-steroidal anti-inflammatory drugs (NSAID) intake (2 tablets/week), oral steroids or steroid enemas intake in the last three months, or initiation of azathioprine treatment within the last three months, infectious colitis and primary immunodeficiency.

We defined clinical remission in UC as a Lichtiger Clinical Activity Index of 3 points or less [8] and endoscopic remission – as Mayo endoscopic subscore of 0. Clinical remission in CD was determined as Crohn`s disease activity index (CDAI) <150 [9], and endoscopic remission - as lack of mucosal lesions (erosions, ulcers, aphthous lesions) on ileocolonoscopy.

All enrolled patients underwent a full medical assessment, including a detailed medical history and physical examination. All therapies taken by the patients before enrollment was recorded.

All IBD patients were followed-up for 36 months for relapses of the disease. We defined as frequently relapsing (≥1/year) patients with at least one relapse per year and as infrequently relapsing those with less than one relapse per year (<1/year). We assessed the effect of the clinical predictors age, duration of disease, sex, and smoking on the frequency of relapses in IBD patients.

Statistical analysis

The statistical analysis was performed using SPSS for Windows, Version 25.0. (SPSS Inc., Chicago, USA). For data analysis, the following statistical methods were used: descriptive statistics for tabular and graphical presentation of results, Mann-Whitney test, Student t-test, and binary logistic regression. The obtained results were assessed as statistically reliable in the threshold level of significance, $p<0.05$.

Ethics approval

The current study was approved by the Ethics Committee of "Tsaritsa Yoanna" University Hospital in Sofia, Bulgaria. Before initiating this study, written informed consent was obtained from all patients. The study protocol conforms 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.

Results

Crohn's disease

The current study enrolled 133 CD patients, of which 69 (52%) were men, and the median age at diagnosis was 41.9 ± 8 (19-81) years. Forty-eight (36%) patients were with an ileal disease (L1), 20 (15%) – with colonic CD (L2), and 65 (49%) with ileocolonic localization (L3). Nineteen (14%) had upper gastrointestinal disease (L4). According to disease behavior – 73 (55%) were with B1, 41 (31%) had structuring disease (B2), and 19 (14%) – penetrating (B3) disease. Eight (6%) were with perianal disease; 99 (74%) of the patients were non-smokers, 30 (23%) – smokers, and 4 (3%) – ex-smokers. The mean duration of the disease was 6.9 years (0.25-40). An overview of the demographic patient characteristics is provided in table I.

Sixty-four (48.1%) of the CD patients were frequently relapsing, and 69 (51.9%) were infrequently relapsing. During the first year of the follow-up, 64 (48.1%) patients relapsed, 25 (18.8%) relapsed within the second year, and 16 (12%) within the third one. Only 24 (18%) patients stayed in deep remission within the three-year follow-up.

Thirty-two from the frequently relapsing CD patients were males, and 32 were females, and from the infrequently relapsing – 33 were males and 36 females. There was no statistically significant difference between the predictor sex and the frequency of relapse ($p=0.802$).

In the frequently relapsing group 46 (71.9%) were non-smokers, 16 (25%) – smokers and 2 (3.1%) – ex-smokers. In the infrequently relapsing group - 53 (76.8%) were non-smokers, 14 (20.3%) – smokers and 2 (2.9%) were ex-smokers. There was no statistically significant difference between the predictor smoking and the frequency of relapse ($p=0.509$).

The mean age of frequently relapsing CD patients was 37.8±14.2 years (19-72) and 45.1±14.8 years (23-81) for the infrequently relapsing. There was a significant association between the age and the frequency of relapse ($p=0.001$) (Table II). The binary logistic regression for quality assessment of the predictor age for relapse occurrence showed odds ratio (OR) of 0.964 (95% CI 0.941-0.987, $p=0.002$).

The mean duration of the disease in frequently relapsing patients was 2.9±3.9 years (0.2-25) and 10.2±8.7 years (1-40) in the infrequently relapsing patients. There was a significant association between the duration of the disease and the frequency of relapse ($p<0.001$) (Table II). The binary logistic regression for quality assessment of the predictor duration of disease for relapse occurrence showed odds ratio (OR) of 0.740 (95% CI 0.655-0.837, $p<0.001$).

Table I. Patients' demographics.

Characteristics	Crohn's disease	Ulcerative colitis
Number of patients	133	156
Males	69 (52%)	88 (56%)
Age at diagnosis in years, mean ± SD (years)	41.9 ± 8 (19-81)	46.2 ± 8 (18-84)
Disease duration, mean ± SD (years)	6.9 years (0.25-40)	7.9 years (0.25-45)
Smoking	Non-smokers – 99 (74%) Smokers – 30 (24%) Ex-amokers – 4 (3%)	Non-smokers – 122 (78%) Smokers – 28 (18%) Ex-amokers – 6 (4%)
Location of disease	L1 (ileal) – 48 (36%) L2 (colonic) – 20 (15%) L3 (ileocolonic) – 65 (49%) L4 (upper Gi disease) – 19 (14%)	E1 (proctitis) – 27 (17%) E2 (left-sided colitis) – 82 (53%) E3 (extensive colitis) – 47 (30%)
Disease phenotype	B1 (inflammatory) – 73 (55%) B2 (stricturing) – 41 (31%) B3 (penetrating) – 19 (14%) P (perianal disease) – 8 (6%)	-
Relapsing course	Frequently relapsing – 64 (48.1%) Infrequently relapsing – 69 (51.9%)	Frequently relapsing – 72 (46.2%) Infrequently relapsing – 84 (53.8%)
Extraintestinal manifestations	32 (24.06%)	45 (28.85%)
Patients who had surgery	35 (26.32%)	28 (17.95%)
Treatment	None – 11 (8.27%) Immunosuppressive – 107 (80.1%) Biological – 43 (32.3%)	None – 8 (5.13%) Topical 5-ASA – 24 (15.38%) Systemic 5-ASA – 86 (55.13%) Immunosuppressive – 46 (29.49%) Biological – 30 (19.23%)

Table II. Association between the clinical predictors duration of disease and age with the frequency of relapses in patients with Crohn's disease (CD).

Clinical predictor	Relapses	N	Mean (years)	SD	Min	Max	p
Duration of disease	Infrequent	69	10.2	8.7	1.0	40.0	**<0.001**
	Frequent	64	2.9	3.9	0.2	25.0	
Age	Infrequent	69	45.1	14.8	23.0	81.0	**0.001**
	Frequent	64	37.8	14.2	19.0	72.0	

Ulcerative colitis

There were 156 UC patients enrolled in this study, of which 88 (56%) were men, and the median age at diagnosis was 46.2±8 (18-84) years. Twenty-seven (17%) patients were with ulcerative proctitis (E1), 82 (53%) were with left-sided colitis (E2), and 47 (30%) were with extensive colitis (E3). 122 (78%) of the patients were non-smokers, 28 (18%) – smokers, and 6 (4%) – ex-smokers. The mean duration of the disease was 7.9 years (0.25-45). An overview of the demographic patient characteristics is provided in table I.

Seventy-two (46.2%) of the UC patients were frequently relapsing, and 84 (53.8%) were infrequently relapsing. During the first year of the follow-up, 72 (46.2%) patients relapsed, 30 (19.2%) relapsed within the second year, and 26 (16.7%) within the third one. Only 28 (17.9%) patients stayed in deep remission within the three-year follow-up.

Thirty-six from the frequently relapsing UC patients were males, and 36 were females, and from the infrequently relapsing – 45 were males and 39 females. There was no statistically significant difference between the predictor sex and the frequency of relapse (p=0.656).

In the frequently relapsing group 55 (76.4%) were non-smokers, 13 (18.1%) – smokers and 4 (5.5%) – ex-smokers. In the infrequently relapsing group - 67 (79.8%) were non-smokers, 15 (17.8%)– smokers and 2 (2.4%) were ex-smokers. There was no statistically significant difference between the predictor smoking and the frequency of relapse (p=0.896).

Table III. Association between the clinical predictors duration of disease and age with the frequency of relapses in patients with ulcerative colitis (UC).

Clinical predictor	Relapses	N	Mean (years)	SD	Min	Max	p
Duration of disease	Infrequent	84	12.2	9.4	2.0	45.0	**<0.001**
	Frequent	72	2.9	4.2	0.2	31.0	
Age	Infrequent	84	47.9	14.8	24.0	86.0	**0.001**
	Frequent	72	40.3	14.1	18.0	77.0	

The mean age of frequently relapsing UC patients was 40.3±14.1 years (18-77) and 47.9±14.8 years (24-86) for the infrequently relapsing. There was a significant association between the age and the frequency of relapse (p=0.001) (Table III). The binary logistic regression for quality assessment of the predictor age for relapse occurrence showed odds ratio (OR) of 0.964 (95% CI 0.941-0.987, p=0.002).

The mean duration of the disease in frequently relapsing patients was 2.9 ±4.2 years (0.2-31) and 12.2 ±9.4 years (2-44) in the infrequently relapsing patients. There was a significant association between the duration of the disease and the frequency of relapse (p<0.001) (Table III). The binary logistic regression for quality assessment of the predictor duration of disease for relapse occurrence showed odds ratio (OR) of 0.673 (95% CI 0.584-0.776, p<0.001).

Discussion

Our study demonstrates in a relatively large sample of patients that younger age is associated with more frequent relapses. Moreover, the binary logistic regression shows that any increase in age by one year reduces the risk of relapse by 3.6%, both in UC and CD patients. Extensive population studies with a five and 10-year follow-up period for IBD patients also confirm that the young age of diagnosis is strongly related to the course of the disease and the relapse rate [10-12]. Furthermore, it has been shown that patients diagnosed under the age of 40 years frequently relapse [10]. Our data show similar results – patients at average age at diagnosis of 37.8 years for CD and of 40.3 years for UC relapse more frequently.

Other authors demonstrate that the younger age of diagnosis and female sex are associated with more common relapse [13,14]. Bitton et al. show that younger patients with UC, especially at the age of 20-30, relapse more quickly [15]. The more significant number of previous flares is associated with a shorter time to relapse in women, but not in men. In our patients, we found no influence of the predictor sex on the relapse rate, either in CD or UC patients. Apart from the study by Bitton et al., there are not many studies in the world literature that demonstrate the influence of gender on the relapse rate [16].

In the current study, we show that the longer duration of IBD is associated with a lower risk of relapse. The binary logistic regression demonstrates that any increase in disease duration by one year reduces the risk of relapse by 26% in CD patients and by 32.7% in patients with UC. Such data also demonstrate two other studies in UC patients showing that the risk of relapse decreases with time, whereas the risk of complications, including colorectal cancer, increases, especially in the presence of extensive colitis [17,18]. In patients with CD, there is also a relationship between the longer duration of the disease and the less frequency of relapse [19].

Smoking is considered to be one of the strongest predictors of the course of the disease - it has been shown to lead to more severe disease course in CD, whereas surprisingly, it has a protective function in UC and, respectively, non-smokers and ex-smokers have a higher risk of relapse [20,21]. However, we have not found a link between smoking and the frequency of relapse in the followed patients. A possible explanation for that could be the fact that our study was performed in a tertiary IBD centre where cases with more severe disease course are concentrated.

Moreover, the number of smokers in our patients is significantly lower than that of non-smokers, which further complicates the accurate assessment of the effect of the predictor.

Conclusion

We demonstrate in a relatively significant cohort of IBD patients that young age and short duration of the disease are associated with more frequent relapses. Clinical predictors of IBD recurrence are easy to be used in everyday clinical practice and can predict the subsequent course of IBD.

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