BEST: International Journal of Humanities, Arts, Medicine and Sciences (BEST: IJHAMS)
ISSN (P): 2348–0521, ISSN (E): 2454–4728
Vol. 7, Issue 12, Dec 2019, 1–10

STRATIFICATION OF RISK FACTORS FOR SEVERE DISEASE – PART OF THE PERSONALISED APPROACH IN IBD PATIENTS

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ABSTRACT

The current study is on the latest trends in personalised IBD therapy require stratification of disease severity at the onset of the disease.

Objective: Analysis of risk factors for severe disease during the onset of Crohn's disease and ulcerative colitis among young patients at a university clinical centre in Eastern Europe.

Materials and Methods: An analysis of risk factors for severe disease was performed in 186 consecutive IBD patients (111 with Crohn's disease and 75 with ulcerative colitis) aged ≤ 45 years.

Results: Summary data analysis in CD patients selected among those with poor prognostic factors: localisation L1 (36%) and L3 (26%) point to complicated CD, including disabling and requiring surgery progression; behaviour B2 (13.5%), B3 (10%) and perianal disease (13%), almost 60% debut with moderate and severe activity, which suggests a complicated disease, disabling and complicated course, as well as permanent stoma [12,15, 17, 34, 35, 36, 37].

In the group of patients with UC, almost half are men, over 80% are extensively affected (E2 + E3), and almost 60% debut with moderate and severe activity.These characteristics suggest a high risk of relapse and colectomy. 70.96% (n=132/186) of young IBD patients at our centre have a profile characteristic of a severe disease and/or a disease with complications.

Conclusions: Stratification of risk factors of IBD severity at the onset is of great importance for early inclusion of biological treatment, intensive monitoring, through biomarkers, patient report outcomes (PRO's), personalisation of treatment to attempt to change the evolution of the disease and reduce the risk of complications and disability.

KEYWORDS: IBD, Crohn's Disease, Ulcerative Colitis, Risk Factors & Personalised Approach

1. INTRODUCTION

In the era of biological therapy with modern treatment options for IBD patients, it turned out that the initiation and, largely, the termination of a treatment are affected by the individual characteristics of the debut and the disease's course, as well as by the degree of remission achieved.The need to know in detail, the onset and development of the disease in the individual patient is at the foreground [1, 2].

Today, professionals are facing two main questions: when to start the biological therapy and when to end it. These questions are based on the stratification of risk factors of a severe disease [2–6].

2. OBJECTIVE

Personalising therapy requires excellent knowledge of the IBD debut of the individual patient. We set out to analyse the onset of IBD (Crohn's disease - CD and ulcerative colitis - UC) in patients' ≤ 45 years of age and risk factors for severe disease.

3. MATERIAL AND METHODS

An analysis of risk factors for severe disease, based on literature established profile was performed in 186 consecutive IBD patients (111 with CD and 75 with UC) ≤ 45 years of age,at university referral center.CD and UC activity was measured trough to the International definitions of disease activity according to the American College of Gastroenterology, ECCO-consensus, and the Japanese Society of Gastroenterology[7, 8, 9].

The statistical analysis was performed using SPSS for Windows, Version 25.0. (SPSS Inc., Chicago, IL, USA). For data analysis, the following statistical methods were used: descriptive statistics for tabular presentation of results; Continuous variables were summarised using the mean ± standard deviation, Chi-squared test for categorical variables. The level of significance used for all analyses was $p<0.05$.

4. RESULTS

The average age of IBD patients at diagnosis: for patients with CD was 30.95 ± 8.45, and for patients with UC 34.57 ± 8.10, with no statistically significant difference.

According to the Montreal classification, patients with CD with the highest incidence were those with colorectal localisation (L2) 37.84% (n = 42), followed by those with small intestine localisation (L1) 36.00% (n=40), and 26.13% (n=29) combined involvement is observed - ileocolon (L3).In more than half of the patients, the initial phenotypic expression was inflammatory (B1) - 65.80% (n=73), and in 13.50% (n=15) stricturing (B2).Approximately, 10.00% debuted with penetrating form (B3) - 9.91% (n=11). Perianal disease was detected in 12.60% (n=14).

Patients with UC with the highest incidence on debut were those with involvement of the left colon (E2) 57.33% (n=43), followed by coverage of the entire colon (E3) 28.00% (n=21), at 14.67% (n=11) the disease is limited to the rectum - proctitis (E1). (Table 1)

Table 1: Demographic and Clinical Characteristics of IBD Patients

	Crohn's Disease n=111	**Ulcerative Colitis n=75**
Gender		
Male, *n* [%]	59 [53.20]	36 [48.00]
Female, *n* [%]	52 [46.80]	39 [52.00]
Age of complaints onset*[median, range]*	29.19[11- 45]	29.82 [13- 43]
Age at diagnosis *[median, range]*	30.95 [14- 45]	34.57 [19- 45]
Male, *n* [%]	29.05 [14- 45]	34.11 [19- 45]
Female, *n* [%]	33.12 [18- 45]	35.00[19- 45]
Diagnostic delay (months)*[median, range]*	22.63[1-276]	57.29 [1- 252]
Male, *[median, range]*	31.88[1-276]	66.79 [1- 252]
Female, *[median, range]*	14.46[1-144]	47.00 [1- 292]
Disease extent*		
L1[ileum], *n* [%]	40 [36.00]	
L2 [colonic], *n* [%]	42 [37.80]	
L3 [ileocolonic], *n* [%]	29 [26.10]	

Perianal disease, *n* [%]	14 [12.60]	
Proctitis, *n* [%]		11 [14.70]
Left-sided, *n* [%]		43 [57.30]
Extensive colitis, *n* [%]		21 [28.00]
Disease behavior*		
B1 [non-stricturing, non-penetrating], *n* [%]	73 [65.80]	
B2 [structuring], *n* [%]	15 [13.50]	
B3 [penetrating], *n* [%]	11 [9.90]	
Disease activity*/CDAI		
CDAI $\leq$ 150, *n* [%]	16 [14.40]*	
Mild, *n* [%]	20 [18.00]*	16 [21.30]*
Moderate, *n* [%]	53 [47.70]*	35 [46.70]*
Severe, *n* [%]	6 [5.40]*	24 [32.00]*
Existence of pseudopolyps, *n* [%]	-	34 [45.30]*

*International definition of disease activity of Crohn's Disease and Ulcerative Colitis.

In both diseases, patients with moderate IBD activity are predominant.

For patients with CD, BEST index < 150 on debut should be interpreted as a disease with mild symptoms.

In 45.30% (n=34) of UC patients, the initial endoscopic examination found both the presence of acute inflammatory endoscopic changes and pseudopolyposis, which is an evidence of a mucosal inflammation predating the diagnosis.

We have studied and analysed the clinical picture, with which the two diseases begin.In CD, the most common complaints from patients are: abdominal pain - 77.50% (n=86), diarrhoea 64.90% (n=72) and weight loss - 31.50% (n=35).In patients with UC, the leading symptom was haematochezia - 89.30% (n=67), followed by diarrhoea - 73.30% (n=55) and mucus impurities in the faecal masses - 34.70% (n=26). (Table 2)

Table 2: Presenting Symptoms in IBD Patients

	Crohn's Disease n=111	**Ulcerative Colitis n=75**
Abdominal pain, *n* [%]	86 [77.50]	21[28.00]
Diarrhea, *n* [%]	72[64.90]	55 [73.30]
Weight loss, *n* [%]	35 [31.50]	5 [6.70]
Fever, *n* [%]	34 [30.60]	11 [14.70]
Bloody stools, *n* [%]	30 [27.00]	67[89.30]
Mucus in stools, *n* [%]	35 [22.50]	26[34.70]
Fatigue, *n* [%]	20 [18.00]	3 [4.00]
Tenesmus, *n* [%]	-	5[6.70]

In some IBD patients, the disease manifests with an acute surgical abdomen, and in others the onset is associated with multiple syndromes and symptoms. In 52.68% (n=98) we found 3 or more symptoms in the original clinical presentation.

Occurrences of rebound tendernessand/or perianal disease cause 35.10% (n = 39) of patients with CD, to be initially admitted to the surgical ward.

Regardless of the level of CD activity, we have found that the first manifestations of the disease can be accompanied by intestinal complications, such as:ileus/subileus 20.72% (n= 23) and intra-abdominal abscess 12.61% (n=14).The different combination of stricturing and/or penetrating phenotype, perianal disease, and intestinal complications led to operative intervention in 31.50% (n=35) of the patients at the time of the diagnosis.

A summary analysis of the clinical data revealed several types of extra intestinal manifestations (EIMs) occurring in parallel with the onset of IBD, in more than half of our patients (respectively for CD - 52.25% (n=58) and UC - 53.30% (n=40).

In both diseases, the most common EIMs are: iron deficiency anaemia (IDA); IBD, associated arthroapia (IBDAA), followed by malabsorption syndrome (for CD) and other systemic manifestations. (Table 3)

The combination of several EIMs occurred in 20.43% (n=38/186) of IBD patients.Affecting more than one system outside the gastrointestinal tract (GIT) points to a severe disease [4, 7, 10, 11, 12] and defines the difficulties in diagnosing, which is delayed by an average of 41.09 months in IBD patients

Abdominal pain, different in intensity, intermittent diarrhoea, high number of EIMs are referral for a specialist gastroenterologist, and diagnosis of CD take 22.63 months.Episodes of haematochezia alone or in combination with diarrhoea, led to a specification of the diagnosis of UC with an average of 57.29 months.

Table 3: Comparative Analysis of Extraintestinal Manifestations in IBD Patients During the Disease's Onset

	Crohn's Disease n=111		Ulcerative Colitis n=75	
	n	%	n	%
IBD arthropathy	20	18.00	8	10.70
Iron deficiency anaemia	47	42.30	35	46.70
Erythema nodosum	6	5.40	2	2.70
Eye manifestations	1	0.90	2	2.70
Primary sclerosing cholangitis	-	-	1	1.30
Malabsorption syndrome	18	16.20	-	-
Pioderma gangrenosum	1	0.90	-	-
Aphthous stomatitis	4	3.60	-	-

In the group of young patients with CD, a significant percentage has a high inflammatory burden. Moderate activity at the time of the CD diagnosis (CDAI ≥ 220), extensive GIT involvement (L3 + L4), complicated disease (B2, B3, B2 + 3, p), surgery at debut, presence of EIMs, create the profile of a patient at high risk of severe and progressing disease [5, 7, 8, 11, 12, 13, 14, 15, 16, 17].

Moderate to severe activity at the time of CD diagnosis we found in 53, 15% [n=59], extensive GIT involvement-L3- 26.10% [n=29], and complicated disease (B2, B3, B2+3, +p) in 36.03% [n=40].

When analysing the risk factors above for CD patients, we discovered that there are two or more risk factors in 71.17% (n = 79/111), 41.44% (n = 46/111) have only two risk factors, 16.22% (n = 18/111) have three, 9.91% (n = 11/111) have four, and 3.60% (n = 4/111) have 5 risk factors.19.82% (n = 22/111) of patients had a debut of the disease with only one risk factor.

In young patients with UC, the male gender, moderate to severe, extensive involvement, and the presence of EIMs on debut, determine the aggressive course of the disease [12, 17, 18, 19, 20, and 21].

In the group of patients with UC, almost half are men, over 80% are extensively affected (E2 + E3), and almost 60% debut with moderate and severe activity.These characteristics suggest a high risk of relapse and colectomy [19, 20, 22, 23,24,25,26,27,28,29,30,31,32].

We determined that one of these risk factors occurred in 22.66% (n=17/75), respectively, two in 33.33% (n= 25/75), three in 30.66% (n = 23/75), and 6.66% (n=5/75) have four risk factors.

In nearly two thirds of patients with UC (70.66% (n=53/75)), the disease manifests with the presence of two or more of the two described risk factors for an aggressive course.

5. DISCUSSIONS

Because much of the summary analysis of severe and debilitating IBD highlights the role of young age, we selected patients who were diagnosed at ≤ 45 years of age. In both CD and UC, this age defines a complicated, debilitating, recurrent, and requiring surgery disease [12, 14, 16, 17, 33, 34].

Based on the existing literature profile of a severe disease, we selected those CD patients with poor prognostic factors: localisation L1 (36%) and L3 (26%) is associated with complicated CD, including disabling and requiring surgery progression; behaviour B2 (13.5%), B3 (10%) and perianal disease (13%), almost 60% debut with moderate and severe activity, which suggests a complicated disease, disabling and complicated course, as well as permanent stoma [12,15, 17, 34, 35, 36, 37].

The combination of stricturing and/or penetrating phenotype, perianal disease and intestinal complications led to surgery in nearly 1/3 of patients with CD.Surgery at present of CD creates the profile of a patient with complicated disease, impaired quality of life (QoL), disability and work disability [38, 39, 40, and 41].

Although CDAI is widely used to evaluate CD activity, it also has its weaknesses: subjective assessment of the patient, inability to reflect the complex impact and severity of perianal disease [42].

Recent meta-analyses from several studies highlight the poor correlation between CDAI≥ 220 and biomarkers used to follow up on CD patients [33, 43].

The assessment of UC severity, according to the International definitions of disease activity also has its weaknesses.It is symptom based, without covering any other aspects of the severity of the disease [7, 42].

Therefore, strategies such as treat to target emerge, which provide a more comprehensive assessment of IBD activity.

The strategy is based on a combination of: Patients' report outcomes (PRO's), objective inflammation markers such as CRP and FCP, and endoscopic activity [44,45].

Assessing the complex impact that IBD has, we examined the presence of EIMs at the onset of the disease.

More than half of our patients (CD-52.25%, UC-53.30%) have EIMs at diagnosis, and in 1/5 of cases more than one system is affected outside the GIT.EIMs have a significant impact on the severity of the disease, quality of life, delay in diagnosis, and require high competence and the availability of a multidisciplinary team to monitor patients [4, 7, 12, and 46].

Regardless of the number of risk factors identified, each of them, and even more so the combination of several, have a significant impact on the evolution and the severity of the disease.

More than seventy percentage (70.96% (n= 132/186)) of young IBD patients at our centre have a profile characteristic of severe and/or complicated disease. They are well suited for early inclusion of biological treatment, intensive monitoring, through biomarkers, patient report outcomes (PRO's), and personalisation of treatment to attempt to change the evolution of the disease, and reduce the risk of complications and disability [5, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57].

6. CONCLUSIONS

In recent years, many authors [12, 14, 15, 16, 17, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 36, 37, 58] have contributed to the creation of a profile of severe and aggressive disease, whose evolution over time will lead to disabling and worsening QoL. Although IBD are heterogeneous diseases with very different and difficult to predict progression, stratification of risk factors of disease severity at the onset of the disease is of great importance. The inclusion of the subjective sensations of the patient in combination with biochemical, endoscopic and morphological parameters leads to precise monitoring, timely change in the treatment strategy and largely determines the current needs for disease control.Therefore, when starting a therapy, and when deciding to discontinue a treatment, it is always necessary for the clinician to review the risk factors of a severe disease.

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