“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
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MEDICINE

Quality of Life, Anxiety, Depression and Fatigue in Inflammatory Bowel Diseases
PhD THESIS SUMMARY

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TABLE OF CONTENTS

LIST OF PUBLISHED ARTICLES

1. **Stroie T**, Preda C, Meianu C, Croitoru A, Gheorghe L, Gheorghe C, Diculescu M. Health-Related Quality of Life in Patients with Inflammatory Bowel Disease in Clinical Remission: What Should We Look For? Medicina (Kaunas). 2022 Mar 27;58(4):486. doi: 10.3390/medicina58040486.
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2. **Stroie T**, Preda C, Meianu C, Istrătescu D, Manuc M, Croitoru A, Gheorghe L, Gheorghe C, Diculescu M. Fatigue Is Associated with Anxiety and Lower Health-Related Quality of Life in Patients with Inflammatory Bowel Disease in Remission. Medicina (Kaunas). 2023 Mar 9;59(3):532. doi: 10.3390/medicina59030532.
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3. **Stroie T**, Preda C, Istratescu D, Ciora C, Croitoru A, Diculescu M. Anxiety and depression in patients with inactive inflammatory bowel disease: The role of fatigue and health-related quality of life. Medicine (Baltimore). 2023 May 12;102(19):e33713. doi: 10.1097/MD.0000000000033713.
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INTRODUCTION

Inflammatory Bowel Diseases (IBD), with the two subtypes: Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions of the digestive tract and have a remitting-relapsing evolution, with periods of active disease that alternate with periods of remission.

Due to the unpredictable nature of IBD, the symptoms that can sometimes be debilitating, with persistent episodes of diarrhea, abdominal pain, joint pain, and concerns about long-term outcomes, patients suffering from these conditions may have a lower quality of life, and may suffer from anxiety, depression or fatigue.

Although neglected in the past, nowadays the health-related quality of life (HR-QoL) is becoming more and more important, its improvement becoming one of the main end-points in most clinical trials with the molecules. In addition, the collection of patient reported outcomes (PRO) has become a common practice, both in clinical practice and in clinical trials.

Most studies that analyze the HR-QoL, anxiety, depression, or fatigue include patients with both active and inactive IBD, as well as patients with extraintestinal manifestations, perianal involvement, or various other comorbidities. It is well known that active disease is associated with a significant decrease in the HR-QoL and with the occurrence of symptoms of anxiety, depression or fatigue.

For this reason, the studies carried out in this thesis focused on patients with IBD in remission, without any other significant comorbidities, without extraintestinal manifestations and without perianal involvement. The patients enrolled in these studies were considered to be optimally treated and did not require changes in treatment or other therapeutic interventions.

The premise of these studies was that even these patients, although they are in remission, may still have a lower HR-QoL and may still face anxiety, depression or fatigue.

The aim of the thesis is to analyze these aspects, as well as the complex interrelationship between HR-QoL, anxiety, depression and fatigue, to identify the factors they are associated with, and to estimate their prevalence among patients with inactive IBD.

The enrolled patients were treated in the Gastroenterology and Hepatology Department of the Fundeni Clinical Institute in Bucharest, within the Center for Patients with Inflammatory Diseases. Patients were enrolled between March 2021 and December 2022

and were in remission for at least 3 months at the time of enrollment. Patients were administered a series of questionnaires to assess the HR-QoL, the level of fatigue, and the presence of symptoms of anxiety and depression: IBDQ, FACIT-F, and HADS. Demographic data, data related to the evolution of the disease, treatment or lifestyle were collected based on a short interview and from the hospital's electronic records.

The main results obtained show that decreased HR-QoL is associated with anxiety, fatigue and exposure to a greater number of biological agents. Fatigue was identified in 38.7% of patients, and was associated with lower HR-QoL, with anxiety, with female gender and with longer disease duration. Anxiety and depression have an increased prevalence: 34.1% and 18.2%, respectively. However, it was found that most patients had only mild forms (68.9% of patients with anxiety and 91.7% of patients with depression). Both anxiety and depression, analyzed individually, are associated with fatigue. In addition, anxiety is associated with lower HR-QoL and depression with exposure to a greater number of biological treatments.

These are the first studies conducted in Romania that analyze these elements as well as their complex interrelationship. The obtained results are relevant and could have clinical implications. The identification and the control of the factors that are associated with the deterioration of the HR-QoL, the increased awareness of the important prevalence of anxiety and depression and their proper management, as well as the diagnosis and investigation of fatigue could lead to a significant improvement in the patients' psychosocial status, and could even improve the evolution of the intestinal disease.

However, due to the fact that this study has a cross-sectional design, a causal relationship between the analyzed elements could not be established. It is also possible that the included patients, being treated in a tertiary gastroenterology center, had a more severe form of the disease. Disease remission was determined on clinical grounds only and confirmed by inflammatory markers within normal limits (CRP <5 mg/l and faecal calprotectin <150ug/g), without performing colonoscopies at enrollment.

Expanding this type of research, developing multicenter studies that analyze these issues and enroll larger numbers of patients, and including patient-reported outcomes in national registries could provide additional information of interest to both physicians and patients.

ORIGINAL PART

1. Introduction

Patients with IBD have a lower HR-QoL compared to the general population and are more frequently affected by anxiety, depression and fatigue.

The three studies evaluate the HR-QoL, fatigue, anxiety and depression in patients with IBD who are in clinical and biochemical remission, without disease complications and who do not require changes in the therapeutic management, the patients included in these studies being considered to be optimally treated.

The aim of the first study is to assess the HR-QoL and to identify the factors associated with its deterioration.

The second study analyzes the prevalence of fatigue and identifies factors associated with it.

The third study evaluates anxiety and depression and assesses their severity and prevalence. It also identifies the factors that are associated with these conditions.

2. Materials and Methods

The three studies have a cross-sectional design and are observational, single-center studies.

Inclusion criteria: expressing consent to participate in the study, age >18 years, diagnosis of IBD (CD or UC) with histological confirmation for at least 3 months, corticosteroid-free clinical remission (defined according to the activity scores described below) for at least 3 months, biochemical remission: value of the last fecal calprotectin (within the last 6 months) <150 ug/g; value of the C-reactive protein (CRP) at the time of inclusion <5 mg/l.

Exclusion criteria: inability to understand the informed consent, inability to understand and complete the questionnaires, current treatment with corticosteroids, presence of perianal disease, presence of extraintestinal manifestations, presence of ostomy, presence of symptomatic strictures in patients with CD, presence of other comorbidities that in the opinion of the investigator could impact the HR-QoL, presence of previously diagnosed

mental disorders, participation in clinical trials with experimental treatments, pregnancy in female patients.

The following scores were used to assess disease activity:

- Harvey Bradshaw Index (HBI) for CD
- Simple Clinical Colitis Activity Index (SCCAI) for UC

Remission was defined for values of HBI ≤4 points and SCCAI ≤1 point.

In addition, all included patients had the last fecal calprotectin value (within the last 6 months) <150 ug/g and CRP <5 mg/l.

The patients were asked to fill in the following self-administered questionnaires:

- Inflammatory Bowel Disease Questionnaire (IBDQ)-32
- Hospital Anxiety and Depression Scale (HADS)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

Patients were considered to have symptoms of anxiety or depression at values of the HADS-A score >7 points or HADS-D >7 points, respectively. Fatigue was considered for FACIT-F values ≤40 points.

Hemoglobin (Hb) and CRP values used in this study are resulted from the blood sample routinely collected during the hospital visit.

Anemia was considered for Hb values <12 g/dl for women and <13 g/dl for men.

Information on demographics, disease characteristics, treatments, or lifestyle was collected through a brief interview and from the hospital's electronic records.

Statistical analysis was performed using R 4.1.2 (1 November 2021) (©2021 The R Foundation for Statistical Computing).

Statistical significance was established for values of $p < 0.05$.

The studies were approved by the Ethics Committee of the Fundeni Clinical Institute.

All patients received detailed information regarding the procedures and purpose of these studies. They were assured of the confidentiality of their data. All patients who expressed their intention to participate signed the informed consent form before any other study procedure was performed.

1st Study:

Health-related Quality of Life in Patients with Inflammatory Bowel Disease in Remission

A number of 110 consecutive patients diagnosed with IBD that were in corticosteroid-free remission for more than 3 months and met the eligibility criteria were invited to participate in this study. Out of them, 103 agreed to participate and signed the informed consent form. Six patients were excluded due to incomplete data. Finally, 97 patients were enrolled in the study.

1. Results

Data regarding the characteristics of the study population are presented in Table 1.

Characteristic	
Gender - Male, n (%) - Female, n (%)	 62 (63,9%) 35 (36,1%)
Phenotype - CD, n (%) - UC, n (%)	 65 (67%) 32 (33%)
Median patient age, years (IQR)	39 (29 – 47)
Active smokers, n (%)	30 (30.9%)
Median disease duration, years (IQR)	5 (2 – 10)
Treatment - Biologic, n (%) - Conventional, n (%)	 93 (95.9%) 4 (4.1%)
Type of biological treatment - Infliximab - Adalimumab - Vedolizumab - Ustekinumab	 55 (56.7%) 10 (10.3%) 26 (26.8%) 2 (2%)
Number of biological tratments - 0-1, n (%) - >1, n (%)	 75 (77.3%) 22 (22.7%)
History of IBD-related surgery	31 (31.9%)
Level of education - Low, n (%) - Medium, n (%) - High, n (%)	 6 (6.2%) 43 (44.3%) 48 (49.5%)
Anemia, n (%)	10 (10.3%)
Mean IBDQ score (+/- SD)	190.54 (+/- 22.7)
FACIT-F score - Mean (+/- SD) - Severe fatigue, n (%) (FACIT-F <30)	 42.25 (+/- 8.2) 6 (6.2%)
Symptoms of anxiety, n (%)	32 (33%)
Symptoms of depression, n (%)	16 (16.5%)

Table 1. Characteristics of the study population

IBDQ-32 scores were compared across different variables in order to identify factors associated with a lower HR-QoL.

Both univariate and multivariate analysis data are shown in Table 2.

	Univariate analysis		Multivariate analysis
	Mean IBDQ	***p* value**	***ß coef.; p* value**
Gender • Male • Female	194.9 182.7	0.016	β=-1.21; p=0.60
Patient age	Correlation r=-0.002	0.97	β=0.07; p=0.43
Phenotype • CD • UC	186.9 197.81	0.007	β=2.91; p=0.27
Disease duration	Correlation r=-0.24	0.017	β=-0.18; p=0.43
Number of biological treatments • 0-1 • >1	196.38 170.63	<0.001	β=-7.25; p=0.02
History of IBD-related surgery • Yes • No	186.41 192.48	0.24	β=3.66; p=0.15
Level of education • Low • Medium • High	181.33 191.86 190.52	0.69	β=1.39; p=0.43
Anemia • Yes • No	169.6 192.95	0.02	β=-0.07; p=0.98
FACIT-F score	Corelație r=0.89	<0.001	β=1.90; p<0.001
Symptoms of anxiety • Yes • No	166.93 202.16	<0.001	β=-11.38; p<0.001
Symptoms of depression • Yes • No	162.87 196.01	<0.001	β=2.59; p=0.49

Table 2. Univariate and multivariate analysis

In the univariate analysis, the following factors were associated with a lower HR-QoL: female gender, CD phenotype, longer disease duration, multiple biological therapies, anemia, fatigue, anxiety and depression.

In the multivariate analysis, among all the factors that were analyzed in the univariate analysis, the following factors remained significantly associated with a lower HR-QoL: symptoms of anxiety (p<0.001), fatigue (p<0.001) and exposure to more than one biological agent (p=0.02).

No statistically significant differences were found between the IBDQ-32 score values obtained by patients treated with different biological agents.

Type of biological treatment	Mean IBDQ score	*p* value
Infliximab	195.67	0.051
Adalimumab	183	
Vedolizumab	185.07	
Ustekinumab	159	

Table 3. Mean values of the IBDQ-32 score according to the type of biological treatment

Next, a multivariate analysis was performed in order to identify the factors that influence the values of the IBDQ-32 domains (Table 4).

These factors may impact of the HR-QoL by impairig certain domains comprised in the IBDQ score, but they may not have a significant impact on the total score.

	IBDQ B Bowel symptoms (β coef.; p)	IBDQ S Systemic symptoms (β coef.; p)	IBDQ E Emotional function (β coef.; p)	IBDQ SF Social function (β coef.; p)
Gender	β=0.53; p=0.60	β=-0.11; p=0.82	β=-0.26; p=0.81	β=-1.37; p=0.054
Patient age	β=-0.02; p=0.47	β=0.06; p=0.004	β=0.09; p=0.04	β=-0.04; p=0.09
Phenotype	β=1.57; p=0.18	β=-0.37; p=0.51	β=0.75; p=0.56	β=0.96; p=0.22
Disease duration	β=0.01; p=0.87	β=0.05; p=0.29	β=-0.21; p=0.06	β=-0.04; p=0.56
>1 biological therapies	β=-1.94; p=0.16	β=-0.54; p=0.51	β=-1.25; p=0.41	β=-3.60; p<0.001
History of IBD-related surgery	β=1.94; p=0.09	β=0.04; p=0.93	β=2.37; p=0.06	β=-0.69; p=0.37
Level of education	β=0.84; p=0.28	β=-0.04; p=0.90	β=0.06; p=0.94	β=0.52; p=0.33
Anemia	β=3.08; p=0.06	β=0.47; p=0.55	β-3.75; p=0.03	β=0.12; p=0.91
FACIT-F score	β=0.40; p<0.001	β=0.38; p<0.001	β=0.80; p<0.001	β=0.31; p<0.001
Symptoms of anxiety	β=-1.80; p=0.19	β=-1.67; p=0.01	β=-8.25; p<0.001	β=0.34; p=0.71
Symptoms of depression	β=1.60; p=0.33	β=0.28; p=0.72	β=-0.98; p=0.59	β=1.68; p=0.14

Table 4. Analysis of factors that influence the IBDQ-32 domains

The values of the FACIT-F fatigue score correlated with the values of all domains of the IBDQ-32 score: bowel symptoms, systemic symptoms, emotional function and social function.

This means that patients affected by fatigue (lower values of the FACIT-F score) also recorded lower values of all the domains of the IBDQ-32 score, having a lower HR-QoL.

Age is positively associated with the values of the following domains of the IBDQ-32 score: systemic symptoms, emotional function.

Younger patients tend to score lower in these domains.

Patients exposed to several lines of biological treatment (patients who performed at least one switch) had lower values of the social function domain, this association being highly statistically significant ($p<0.001$), with a value of $\beta=-3.60$.

Patients with anemia had lower values of the emotional function domain, all the other domains not being impacted by the presence of anemia.

The presence of anxiety symptoms strongly and significantly impacts the emotional function ($\beta=-8.25$, $p<0.001$). In addition, these symptoms are associated to a lesser extent with lower values of the systemic symptoms domain ($\beta=-1.67$, $p=0.01$). On the other hand, the presence of depressive symptoms did not impact any of the domains of the IBDQ-32 score.

2. Conclusions

The HR-QoL of IBD patients in remission is significantly impacted by fatigue and anxiety. Patients who have been exposed to multiple lines of biological treatments also have a significantly lower HR-QoL.

The patients included in this study were considered to be optimally treated, and had no indication for endoscopic investigations or other therapeutic interventions. This study highlights the fact that even these patients may have a lower HR-QoL. By identifying these factors and acting on them, the quality of life of these patients could be improved.

Further studies are needed to prospectively analyze how the HR-QoL could be improved by acting on these factors. Multicenter studies with a larger number of patients are needed to allow the analysis of a larger number of factors that may influence the HR-QoL.

2nd Study:

Fatigue in Patients with Inflammatory Bowel Disease in Remission

A number of 141 consecutive patients diagnosed with IBD that were in corticosteroid-free remission for more than 3 months and met the eligibility criteria were invited to participate in this study. Out of them, 130 agreed to participate and signed the informed consent form. Eight patients were excluded due to incomplete data. Other three patients had proof of endoscopic activity and were not included. Finally, 119 patients were enrolled in the study.

1. Results

Data regarding the characteristics of the study population are presented in Table 1.

Characteristic		
Gender	Male, n (%) Female, n (%)	72 (60.5%) 47 (39.5%)
Median patient age, years (IQR)		39 (30–47)
Phenotype	CD, n (%) UC, n (%)	77 (64.7%) 42 (35.3%)
Median disease duration, years (IQR)		6 (2–10)
Active smokers, n (%)		41 (34.5%)
Treatment	Biological, n (%) Conventional, n (%)	105 (88.2%) 14 (11.8%)
Type of biological treatment	Infliximab, n (%) Adalimumab, n (%) Vedolizumab, n (%) Ustekinumab, n (%)	53 (50.5%) 13 (12.3%) 34 (32.4%) 5 (4.8%)
Number of biological treatments	0–1, n (%) >1, n (%)	91 (76.4%) 28 (23.5%)
History of IBD-related surgery, n (%)		37 (31.1%)
Anemia, n (%)		17 (14.3%)
Level of education	Low, n (%) Medium, n (%) High, n (%)	8 (6.7%) 48 (40.3%) 63 (52.9%)
Employed, n (%)		100 (84%)
FACIT-F	Mean (± SD) Fatigue (FACIT-F ≤40), n (%)	41.6 (±8.62) 46 (38.7%)
Mean IBDQ score (± SD)		189.4 (±24.1)
Symptoms of anxiety, n (%)		44 (37%)
Symptoms of depression, n (%)		25 (21%)

Table 1. Characteristics of the study population

2. Univariate analysis. Analysis of the FACIT-F score

The analysis of the FACIT-F fatigue score is presented in Table 2 and Table 3.

		Mean FACIT-F score (±SD)	*p* value
Gender	Male Female	43.9 (7) 38.3 (9.6)	<0.001
Phenotype	CD UC	41 (9.2) 42.9 (7.1)	0.19
Active smoking	Yes No	42.2 (8.2) 41.4 (8.7)	0.61
Level of education	Low Medium High	38.6 (5.3) 42.6 (8.3) 41.4 (9)	0.94
>1 biological therapy	Yes No	37.2 (9.7) 43.1 (7.7)	0.004
Unemployment	Yes No	41.8 (8.2) 41.7 (8.6)	0.96
Anemia	Yes No	34.6 (11) 42.9 (7.5)	0.008
History of IBD-related surgery	Yes No	40.1 (9.8) 42.4 (7.8)	0.18
Anxiety	Yes No	34.6 (7.9) 45.7 (5.9)	<0.001
Depression	Yes No	32.8 (7.3) 43.9 (7.4)	<0.001

Table 2. Univariate analysis of the FACIT-F score. Mean FACIT-F score

Table 3 shows the correlation between FACIT-F score and age, disease duration and HR-QoL (IBDQ-32 score).

	Correlation with FACIT-F score	*p* value
Patient age	r=-0.04 (95% CI: -0.21 – 0.13)	0.63
Disease duration	r=-0.24 (95% CI: -0.40 – -0.07)	0.005
HR-QoL (IBDQ-32 score)	r=0.82 (95% CI: 0.75 – 0.87)	<0.001

Table 3. Univariate analysis of the FACIT-F score. Correlation of the FACIT-F score

Significantly lower values of the FACIT-F score were identified for the following categories: female gender, multiple biological therapies, anemia, anxiety and depression. FACIT-F score correlated significantly with disease duration (weak negative correlation) and with HR-QoL (strong positive correlation).

3. Univariate analysis. Analysis of fatigue

For this analysis, the cut-off value of 40 points for the FACIT-F score was used. Patients were considered to be affected by fatigue at FACIT-F score values ≤40 points.

The analysis of fatigue according to various variables is presented in Table 4.

	Fatigue		Semnificație (p)
	Yes (FACIT-F ≤40)	No (FACIT-F >40)	
Median age, years (±SD)	39.1 (13.1)	40.2 (12.2)	0.66
Female gender, n (%)	27 (57.4)	20 (42.6)	0.001
CD phenotype, n (%)	34 (44.2)	43 (55.8)	0.14
Median disease duration, years (±SD)	8.9 (8.4)	6.1 (4.9)	0.04
Active smoking, n (%)	16 (39)	25 (61)	0.86
Lower education level, n (%)	6 (75)	2 (25)	0.04
>1 biological therapy, n (%)	18 (64.3)	10 (35.7)	0.003
Unemployment, n (%)	8 (42.1)	11 (57.9)	0.86
Anemia, n (%)	12 (70.6)	5 (29.4)	0.005
History of IBD-related surgery, n (%)	16 (43.2)	21 (56.8)	0.62
Symptoms of anxiety, n (%)	35 (79.5)	9 (20.5)	<0.001
Symptoms of depression, n (%)	22 (88)	3 (12)	<0.001
HR-QoL, mean IBDQ-32 score (±SD)	168.5 (21.4)	202.6 (14.3)	<0.001

Table 4. Univariate analysis of factors associated with fatigue

The following factors were significantly associated with fatigue: female gender, longer disease duration, lower education level, >1 biological therapy, anemia, symptoms of anxiety, symptoms of depression, lower HR-QoL.

4. Multivariate analysis

Factors that had a p value <0.2 in the univariate analysis when fatigue was analyzed qualitatively (defined as FACIT-F score value ≤40) were analyzed in a logistic regression model (Table 5).

	OR of fatigue (95% CI)	*p* value
Female gender	3.32 (1.02–10.76)	0.04
CD phenotype	4.67 (0.89–24.37)	0.11
Longer disease duration*	1.13 (1.01–1.27)	0.04
Lower education level	4.05 (0.27–60.01)	0.30
>1 biological therapy	1.13 (0.24–5.31)	0.87
Anemia	5.16 (0.54–48.45)	0.15
Symptoms of anxiety	5.04 (1.20–21.22)	0.008
Symptoms of depression	1.98 (0.32–11.99)	0.45
Lower HR-QoL†	2.21 (1.42–3.44)	<0.001

Tabelul 5. Multivariate analysis of factors associated with fatigue
*one year increase
†10 points decrease in IBDQ-32 score

In the multivariate analysis, the following factors remained significantly associated with fatigue: lower HR-QoL ($p<0.001$), symptoms of anxiety ($p=0.008$), female gender ($p=0.04$), longer disease duration ($p=0.04$).

5. Conclusions

This study highlights the fact that fatigue has a significant prevalence even in patients with inactive disease. In addition, factors associated with fatigue were identified: lower HR-QoL, anxiety, female gender and longer disease duration.

Due to the complex and multifactorial nature of fatigue, further multicenter studies that should include a larger number of patients would be needed in order to identify more predictive or etiologic factors of fatigue in patients with BII.

Prospective interventional studies are needed to evaluate the way fatigue could be improved by acting on these factors.

3rd Study:
Anxiety and Depression in Patients with Inflammatory Bowel Disease in Remission

A number of 150 consecutive patients diagnosed with IBD that were in corticosteroid-free remission for more than 3 months and met the eligibility criteria were invited to participate in this study. Out of them, 135 agreed to participate and signed the informed consent form. Three patients were excluded due to incomplete data. Finally, 132 patients were enrolled in the study.

1. Results

Data regarding the characteristics of the study population are presented in Table 1.

Characteristic		
Gender	Male, n (%) Female, n (%)	76 (57.6) 56 (42.4)
Phenotype	CD, n (%) UC, n (%)	83 (62.9) 49 (37.1)
Median patient age, years (IQR)		38 (30 – 47)
Median disease duration, years (IQR)		6 (2 – 10)
Active smoking, n (%)		47 (35.6)
Treatment	Biologics/small molecules, n (%) Conventional, n (%)	113 (85.6) 19 (14.4)
Type of biological/small molecule treatment	Infliximab, n (%) Adalimumab, n (%) Vedolizumab, n (%) Ustekinumab, n (%) Tofacitinib, n (%)	51 (45.1) 19 (16.8) 35 (31) 7 (6.2) 1 (0.9)
Number of biological treatments	0-1, n (%) >1, n (%)	98 (74.2) 34 (25.8)
History of IBD-related surgery, n (%)		42 (31,8)
Anemia, n (%)		21 (15.9)
Level of education	Low, n (%) Medium, n (%) High, n (%)	10 (7.6) 46 (34.8) 76 (57.6)
Unemployment, n (%)		22 (16.6)
Mean FACIT-F score (± SD)		41.1 (8.9)
Fatigue, n (%) (FACIT-F ≤40)		55 (41.7)
Mean IBDQ-32 score (± SD)		187.9 (23.9)
Anxiety (HADS-A >7 puncte)	Total, n (%) Mild (8-10), n (% of total) Moderate to severe (11-21), n (% of total)	45 (34.1) 31 (68.9) 14 (31.1)
Depression (HADS-D >7 puncte)	Total, n (%) Mild (8-10), n (% of total) Moderate to severe (11-21), n (% of total)	24 (18.2) 22 (91.7) 2 (8.3)

Tabelul 1. Characteristics of the study population

The results of the univariate and multivariate analysis are expressed as OR in Table 2.

	Anxiety						Depression					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.00	0.99–1.01	0.69	-	-	-	1.00	0.99-1.01	0.58	-	-	-
Female gender	2.25	1.08–4.70	0.04	1.19	0.38–3.71	0.76	3.4	1.33–8.65	0.01	1.74	0.53–5.64	0.35
CD phenotype	2.39	1.07–5.34	0.04	2.44	0.61–9.79	0.20	0.79	0.32–1.95	0.78	-	-	-
Longer disease duration	1.01	0.99–1.01	0.16	0.94	0.86–1.03	0.20	1.01	0.99-1.02	0.06	1.01	0.95–1.08	0.66
Active smoking	1.53	0.73–3.23	0.34	-	-	-	1.37	0.55–3.38	0.65	-	-	-
Unemployment	1.78	0.69–4.53	0.22	-	-	-	1.00	0.26–3.03	0.93	-	-	-
>1 biological therapy	1.51	0.67–0.38	0.42	-	-	-	3.90	1.54–9.87	0.006	3.33	1.01–10.97	0.04
History of IBD-related surgery	2.03	0.95–4.34	0.09	2.82	0.59–13.48	0.19	1.69	0.68–4.21	0.36	-	-	-
Anemia	1.23	0.46–3.23	0.86	-	-	-	3.65	1.30–10.21	0.02	1.25	0.32–4.80	0.74
Lower level of education	3.19	0.85–11.96	0.08	0.41	0.05–3.00	0.38	3.4	0.87–13.15	0.08	2.09	0.36–11.86	0.40
Fatigue	17.72	7.03–44.64	<0.001	4.39	1.22–15.79	0.02	25	5.55–112.52	<0.001	9.70	1.67–56.27	0.01
Lower HR-QoL*	2.56	1.91–3.67	<0.001	2.46	1.70–3.91	<0.001	1.59	1.31–1.99	<0.001	1.20	0.91–1.58	0.19

Table 2. Univariate and multivariate analysis of factors associated with anxiety and depression
*10 points decrease in IBDQ-32 score

The following factors were significantly associated with anxiety in the univariate analysis: female gender, CD phenotype, fatigue, lower HR-QoL.

The following factors were significantly associated with depression in the univariate analysis: female gender, multiple biological therapies, anemia, fatigue, lower HR-QoL.

The following factors remained significantly associated with anxiety in the multivariate analysis:

- Fatigue (OR 4.39; 95% CI: 1.22–15.79; p=0.02)
- Lower HR-QoL (OR 2.46; 95% CI: 1.70–3.91; p<0.001)

The following factors remained significantly associated with depression in the multivariate analysis:

- Fatigue (OR 9.70; 95% CI: 1.67–56.27; p=0.01)
- Multiple biological therapies (OR 3.33; 95% CI: 1.01–10.97; p=0.04)

2. Conclusions

Anxiety and depression have increased prevalences in patients with IBD, even during periods of remission.

Fatigue is associated with both anxiety and depression. In addition, anxiety is associated with decreased HR-QoL, and depression is associated with multiple lines of biological therapy.

Early diagnosis and treatment of these conditions, as well as the identification of the factors they are associated with, could have beneficial consequences for patients. There is already evidence that the proper management of these comorbidities is also associated with a favorable evolution of the intestinal disease.

Further studies should have a prospective, multicenter design and should enroll a larger number of patients in order to identify more predictive factors for anxiety and depression. Prospective, interventional studies should analyze various therapeutic approaches and their effect on both psychological impairment and IBD.

Conclusions and Personal Contributions

Patients enrolled in this study were in corticosteroid-free clinical and biochemical remission, had inflammatory markers within normal limits, and had no complications of inflammatory bowel disease or other significant comorbidities requiring therapeutic interventions.

The three studies showed that there is a close and interdependent relationship between quality of life, anxiety and fatigue in this group of patients, the three influencing each other.

Decreased HR-QoL is associated with fatigue, anxiety, and exposure to multiple biological therapies. However, multiple lines of biological treatment can be seen as a marker of disease severity, as these patients had repeated disease relapses that required therapy optimization or switch.

Fatigue has a significant prevalence in patients with IBD in remission (38.7%) and is associated with decreased HR-QoL, anxiety, female gender and longer disease duration.

Identifying the etiological factors of fatigue (e.g. malnutrition, nutritional deficiencies, vitamin or micronutrient deficiencies, side effect of IBD medication, sleep disorders, etc.) and their correction could favorably influence the level of fatigue and implicitly the HR-QoL of these patients.

Anxiety and depression have increased prevalences in IBD patients in remission: 34.1% and 18.2%. However, 68.9% of patients with anxiety and the vast majority of patients with depression (91.7%) had mild forms, according to the HADS questionnaire.

In the 3rd study, both anxiety and depression, analyzed individually, were associated with fatigue. In addition, anxiety was also associated with decreased HR-QoL and depression was associated with multiple lines of biological therapy.

It seems that in this group of patients, the association between depression and decreased HR-QoL is not a significant one. This may be because the number of patients with depression was smaller than that of patients with anxiety, and in addition, the vast majority of patients with depression had mild forms. Thus, depression may have had a limited impact on the patients' HR-QoL.

The concept of psychological remission in IBD is becoming increasingly important and should also be considered as a therapeutic target. Both anxiety and depression have high prevalences in patients with IBD, even in those in remission. Their identification and appropriate treatment is not only associated with a significant improvement in the HR-QoL

and the psychosocial status of the patients, but can also be followed by a more favorable evolution of the intestinal disease.

Further studies should prospectively analyze the interaction between these factors, and the way HR-QoL could be improved by acting on anxiety, depression or fatigue. Multicenter studies with larger numbers of patients are needed in order to identify and analyze more predictive factors.

The three studies represent author's personal contribution.

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