# Inflammatory bowel disease and depressive symptoms: the prevalence and factors associated with depression in patients with inflammatory bowel disease on intravenous biological therapy – single center experience

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**Abstract.** – OBJECTIVE: Depression is one of the most commonly occurring psychiatric comorbidities in patients suffering from inflammatory bowel disease (IBD). This study aims to determine prevalence and risk factors for the more severe symptoms of depression (DP) in IBD patients on intravenous biological therapy (IBT).

PATIENTS AND METHODS: The study consisted of 90 IBD patients who completed a Patient Health Questionnaire—9 (PHQ9) to detect symptoms of depression. Demographic information and disease characteristics were collected as well as medication information for these patients. Univariate and multivariate ordinal logistic regression was done to identify risk factors for the DP.

**RESULTS:** Anti-TNF therapy comprised 58.9% of patients and anti-integrin 41.1%. The prevalence of DP (PHQ9score ≥10) among these patients is 20%. For the univariate logistic regression DP was statistically significantly associated with disease activity (OR 6.656; 95% CI 2.576-17.19, p<0.001), use of corticosteroids (OR 4.224; 95% CI 1.658-10.76, p = 0.003) and thiopurine (OR 2.502 95% CI 1.031-6.069, p = 0.042), as well as relationship status (single, in relationship or married) (OR 0.391; 95% CI 0.173-0.885, p = 0.024). The multivariate analysis indicated that the risk of developing DP was associated with disease activity (OR 5.708; 95% CI 2.138-15.23, p = 0.001).

CONCLUSIONS: Our study shows that most of severe symptoms of depression were present in 20% of the IBD patients examined who were receiving intravenous biological therapy. Particular attention and efforts should, therefore, be focused on patients who have an active form of the disease.

Key Words:
IBD, Depression, Biological therapy.

### Introduction

Essentially, inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract, a consequence of a complex interplay between diverse factors (genetic, developmental, and environmental)<sup>1</sup>. The prevalence of depression (DP) in patients suffering from IBD ranges from 15% to 30%<sup>2</sup>. According to a World Mental Health Survey, this percentage is much higher compared to a 7-17% lifetime prevalence of major depressive disorders, reported in the general population in the United States and the world-wide frequency of 9.8-15.8% for mood disorders<sup>2</sup>.

Symptoms of depression are associated with a deep sense of sadness and a depressed mood, accompanied by problems eating, sleeping, and being motivated to carry out daily tasks. In addition, they often have suicidal thoughts. Anxiety is an irrational fear and tension, which limits the patient in daily activities. Physical symptoms of sweating, palpitations, weakness, decreased concentration and fatigue may also develop<sup>3</sup>.

Symptoms of depression and anxiety reduce one's quality of life <sup>1</sup> and have been linked to more severe IBD symptoms and more frequent IBD flare-ups, increased hospitalization rates as well as lower compliance with treatment<sup>4</sup>.

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A variety of variables have been implicated as risk factors for depression. Some authors have reported that being a female and suffering from an aggressive and active manifestations of IBD were all independently associated with the development of depression in the IBD patients<sup>2</sup>. In a large national Canadian study, depression rates were found to be higher among females and youth, particularly those who reported being single, significantly increased pain and who had functional limitations<sup>5</sup>. Notwithstanding, studies still show no consistency in risk factor results as concerns the development of depression among patients diagnosed with IBD.

Ultimately, it is nigh impossible to truly as certain whether psychological distress influences the severity of gastrointestinal symptoms or gastrointestinal symptoms trigger changes in one mental state that may lead to psychological distress<sup>6</sup>.

Multiple studies have shown that biological therapy may have an effect on reducing depressive symptoms in IBD patients<sup>7,8</sup>. Among those suffering from severe Crohn's disease, treatment using the anti-TNF-alpha drugs infliximab and adalimumab has been associated with a rapid reduction in depression, not attributable solely to reductions in the disease itself<sup>9</sup>.

Yet, among those suffering from IBD, depression and anxiety disorders are commonly underdiagnosed and undertreated. Evertsz' Bennebroek et al<sup>10</sup> have found that only 18% of IBD patients who experience higher levels of anxiety and/or depression received any mental help, while only 21% used any psychotropic medication to treat their depression.

Depression as it relates to IBD is also associated with a decreased adherence to treatment regimens as well as reductions in the short and long-term efficacy of infliximab <sup>11</sup>. Therefore, an understanding of depression risk factors in IBD patients may potentially assist in accurately identifying those most at risk to have poor disease outcomes due to depression<sup>11</sup>.

Bearing the literature in mind, the purpose of this research is to define clinical and socio-demographic risk factors associable with depression in patients undergoing intravenous biological therapy.

# **Patients and Methods**

The study was conducted from January to May 2019 at the Clinical Center of Montenegro, University Center, Referral Center for the Treatment of IBD.

The study consisted of patients older than 18 years of age, who had a pathohistologically confirmed diagnosis of IBD (i.e., Ulcerative Colitis and Crohn's Disease). At the time of the study, all patients were suffering from an aggressive form of the disease and had been receiving biological therapy intravenously (anti-TNFα: infliximab and anti-integrin: vedolizumab) for at least 3 months prior.

Patients receiving subcutaneous biological therapy were excluded from the study, as they had been receiving the therapy prescribed through the Community Health Centers of the cities they reside or had been taking the prescribed drugs, themselves, at home. The study also excluded all patients who may have initiated any pharmacotherapy and/or psychotherapy to treat already existent depression. Patients who regularly used antidepressants and/or anxiolytics therapy due to a history of anxiety and/or depression were also excluded.

Patients of an unclassified IBD were also excluded from the study, along with any expressing a disinterest in participating in the study along with any who were unable to complete the questionnaires on their own.

At their regular appointments at the IBD Unit, patients filled out Patient Health Questionnaire 9 (PHQ9) in order to receive the biological drug. They also filled out a questionnaire to supply data on (1) their demographics (age, gender), (2) habits (smoking), (3) education completed (primary, secondary, tertiary), (4) marital as well as socio-economic status (low, medium, and high) and (5) whether they were actively employed. Screening was also undertaken to record whether they had been taking any other medicine, such as corticosteroids (parenteral, oral, and topical), thiopurines and 5-ASA actively or up to one year prior to participating in the study.

Additional clinical data were obtained either through medical records or in an interview with patients. These data included: 1) age at the onset of IBD (before or after 30 years of age), 2) the total duration of the disease (shorter or longer than 5 years), 3) surgical treatment undertaken and 4) any hospitalization related to IBD problems within the last year.

Quick and easy for patients to complete, the Patient Health Questionnaire (PHQ) is a diagnostic tool for mental health disorders used by health care professionals<sup>12</sup>. The PHQ-9 is a simple test, containing 9 questions. Its overall score ran-

ges from 0 to 27, where a higher result indicates a more severe form of depression. A cut-off of  $\geq$  10 was used to classify severe depression (moderate and severe), which has a sensitivity and specificity of 88% according to the literature<sup>12</sup>. The Serbian version was downloaded from the following site:

(https://www.phqscreeners.com/images/sites/g/files/g10060481/f/201412/PHQ9Serbian%20 for%20Serbia.pdf). The Partial Mayo Index Score (PMIS)<sup>13</sup> was used to assess disease activity in ulcerative colitis (UC) patients in Crohn's disease (CD), the Harvey-Bradshaw Index (HBI)<sup>14</sup> was used. Active disease (moderate and severe) for UC was defined as a PMIS equal to or greater than 5 for CD (moderate and severe), an HBI was equal to or greater than 8.

# Statistical Analysis

IBM SPSS Statistics for Windows, Version 22.0 was used for the statistical analyses (IBM Corp., Armonk, NY, USA). Values are expressed in numbers or percentages as deemed appropriate. The Chi-square test was used for categorical data, while the Fisher's exact test was used for contingency tables, including cells with expected frequencies  $\leq 5$ . Univariate and multivariate ordinal logistic regression was used to evaluate the prediction of depression risk factors in IDB patients. PQH9 scoring according to the implying category (0-4, 5-9, 10-14, 15-19, 20-27) was considered to be a dependent variable. Individual odds ratio (OR) and their 95% confidence intervals (CL) were calculated for each variable separately. A p-value < 0.05 was considered to be statistically significant.

# Results

The study was made up of a total sample of 90 patients (male - 56.7%, female - 43.3%), 48 (53.3%) were UC and 42 (46.7%) CD. Most patients (88.9%) were under the age of sixty, while 71.1% were under the age of thirty at the time of their initial diagnosis.

Based on disease activity scores, 23 patients (25.6%) suffered from an active form of the disease. 14 (60.9%) were UC patients and 9 (39.1) CD. There were no significant statistical differences (p = 0.401,  $\chi^2 = 0.705$ ) between these two groups. A total of 53 (58.9%) patients received anti-TNF therapy, while 37 (41.1%) pa-

tients received anti-integrin therapy. A total of 87.8% had been undergoing biological therapy for more than a year. No statistical significance was found between applied biological therapy type between UC and CD patients (p = 0.161,  $\chi^2 = 1.968$ ).

There was statistical significance in relation to marital status between UC and CD patients (p = 0.044,  $\chi^2 = 4.068$ ). UC were more likely to be in a relationship. There was also a high statistical significance in terms of their surgical treatment: a significantly higher percentage of CD patients underwent surgery compared to UC (p<0.001, FET). Comparisons of UC and CD patient characteristics, disease-related data and data related to other non-biological therapies are provided in Table I.

According to the PHQ9 score, the patients were classified into the following 4 groups: 0-4: 45 (50%); 5-9: 27 (30%); 10-14: 14 (15.6%); 15-19: 4 (4.4%). No patients were classified into the category 20-27. 18 (20%) patients, therefore, met the criteria for more severe forms of depressive symptoms (PHQ9  $\geq$  10) (Figure 1). The characteristics of the IBD patient sample in relation to the value of PHQ9  $\geq$  10 and PHQ9 < 10 are presented in Table II.

Severe symptoms of depression, on a univariate analysis, were statistically significantly associated with disease activity (odds ratio (OR) 6.656; 95% Cl 2.576 - 17.19, p< 0.0001), use of corticosteroids (OR 4.224; 95% Cl 1.658 - 10.76, p = 0.003) and thiopurine (OR 2.502; 95% Cl 1.031 - 6.069, p = 0.042), as well as patient's emotional/marital status (OR 0.391; 95% Cl 0.173-0.885, p = 0.024).

A multivariate analysis showed that the risk for severe depression in patients on intravenous biological therapy is associated with disease activity (OR 5.708; 95% Cl 2.138-15.23, p = 0.001). The results of the univariate and multivariate analyses for risk factors of severe symptoms of depression in IBD patients are given in Table III.

# Discussion

Psychiatric conditions are particularly common among those suffering from chronic medical conditions<sup>1</sup>. Similar to other chronic illnesses, IBD patients are generally more prone to experiencing mental health issues than the overall general population<sup>1</sup>. Yet, although disparate risk factors have been mentioned in the de-

Table I. Differences between UC and CD patients into examine variables.

Variables	Ulcerative colitis	Crohn's disease	<i>p</i> -value	Test
Gender			0.172	χ² 21.862
Male	24 (47.1)	27 (52.9)		χ =====
Female	24 (61.5)	15 (38.5)		
Years	(3 33)	- ()	0.262	$\chi^2 1.252$
< 60	41 (51.2)	39 (48.8)		,,
≥ 60	7 (70)	3 (30)		
Smoking	(4.1)	- ()	0.175	$\chi^2 1.837$
Yes	8 (40)	12 (60)		,,
No	40 (57.1)	30 (42.9)		
In relationship/marriage	(4.1.)		0.044	$\chi^2  4.068$
Yes	35 (61.4)	22 (38.6)		,,
No	13 (39.4)	20 (60.6)		
Employment	15 (5))	20 (00.0)	0.68	$\chi^2 \ 0.170$
Yes	30 (51.7)	28 (48.3)	0.00	λ 0.170
No	18 (56.2)	14 (43.8)		
Education	10 (30.2)	11 (15.0)	0.29	$\chi^2 \ 2.478$
Elementary school	5 (83.3)	1 (16.7)	0.27	λ 2.470
High school	32 (50)	32 (50)		
Faculty	11 (55)	9 (45)		
Socio-economic status	11 (55)	9 (43)	0.352	
	12 (62.2)	7 (36.8)	0.332	$\chi^2 \ 2.089$
Low	12 (63.2)			
Middle	26 (47.3)	29 (52.7)		
High	10 (62.5)	6 (37.5)	0.144	20124
Onset of disease	21 (40.4)	22 (51 6)	0.144	$\chi^2 \ 2.134$
$\leq$ 30 years	31 (48.4)	33 (51.6)		
> 30 years	17 (65.4)	9 (34.6)	0.044	2 0 020
Disease duration	25 (5.4.2)	24 (47.7)	0.844	$\chi^2 \ 0.039$
$\leq$ 5 years	25 (54.3)	21 (45.7)		
> 5 years	23 (52.3)	21 (47.7)		
Surgical treatment			< 0.001	FET
Yes	4 (17.4)	19 (82.6)		
No	44 (65.7)	23 (34.3)		
Hospitalization in last year			0.836	$\chi^{2} 0.43$
Yes	17 (54.8)	14 (45.2)		
No	31 (52.5)	28 (47.5)		
Disease activity			0.401	$\chi^2 0.705$
Active disease	14 (60.9)	9 (39.1)		
Non active disease	34 (50.7)	33 (49.3)		
Biological therapy			0.161	$\chi^2 1.968$
Anti TNF	25 (47.2)	28 (52.8)		
Vedolizumab	23 (62.2)	14 (37.8)		
Corticosteroid	` ′		0.689	$\chi^2 \ 0.16$
Yes	12 (57.1)	9 (42.9)		,,
No	36 (52.2)	33 (47.8)		
Thiopurine	` /	` '	0.897	$\chi^2 \ 0.017$
Yes	12 (52.2)	11 (47.8)		,,
No	36 (53.7)	31 (46.3)		
5 ASA	( )	- ()	< 0.001	FET
Yes	47 (100)	0 (-)		
No		42 (97.7)		
No	1 (2.3)	42 (97.7)		

 $<sup>\</sup>chi^2$  - Chi-square test, FET - Fisher's exact test, PHQ9 - The Patient Health Questionnaire 9, 5 ASA - Aminosalicylates.

velopment of depression in IBD. Across studies, to the best of the authors' knowledge, no papers have, yet, been dedicated depression risk factors in IBD patients receiving intravenous biologic therapy.

In most studies available in the literature, depression is more likely to occur in females<sup>2,5</sup>. Nonetheless, as in a minority of studies<sup>15</sup>, gender was found to have no effect on the depression rate in our study. Likewise, contrary to other studies<sup>5</sup>,

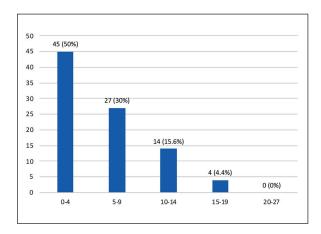


Figure 1. PQH9 scoring of IBD patients in Montenegro.

ours indicated that younger patients were not more likely to show severe symptoms of depression

This study showed a prevalence of depression found in 20% of IBD patients on intravenous biological therapy. Compared to other studies using the same detection method (i.e., the PHQ9 test), higher prevalence percentages were found: 25.8%<sup>16</sup>, 25%<sup>9</sup>, 22.1%<sup>17</sup> to even 34.3%<sup>18</sup>. Additionally, the prevalence of depressive symptoms in most other studies using different testing methods than the PHQ9 generally showed higher values of 25%<sup>1,19</sup>. Other studies have also yielded much lower percentages of - 11%15,20. The difference in the results may likely stem from the differences between the patient groups and the number of respondents. Therein, Neundorf et al<sup>21</sup>, in systemic review conducted in 2016, distinctly noted that the pooled prevalence for depressive symptoms was 21.6% (18.7%, 24.3%) for patients with IBD.

The effect of biological therapy on depression has been thoroughly investigated through a range of studies. Horst and al7 have found that medication treatment for IBD including anti-TNF therapy and immunomodulatory therapy significantly improves depressive symptoms. It also significantly decreases the number of patients who meet criteria of being moderate to severely depressed after a treatment of 1-6 months. Stevens et al<sup>8</sup> also reported anti-TNF biologic therapy and vedolizumab to be associated with significant improvement in symptoms of depression among patients with IBD (within 6 weeks of the initiation of therapy). In a study conducted in a non-IBD sample of depressed individuals resistant to traditional antidepressants, anti – TNF alpha therapy was able to reduce symptoms of depression in patients that had higher inflammatory biomarkers<sup>22</sup>. This exact finding supports our study, as we found that the percentage of depression to be lower even though roughly 60% of patients received anti-TNF therapy.

Earlier studies suggest that patients already suffering from depression and anxiety are more likely to use anti-TNF therapy<sup>19</sup>. It must therefore be noted that patients requiring immunomodulatory and biological therapy are those who suffer from a more aggressive form of the disease. For this very reason, they also have an increased risk for comorbid anxiety and depression related to their disease severity of IBD<sup>2,23</sup>.

The multivariate statistical analysis of our study indicates the most significant factor in the development of severe depression to be disease activity. This result is corroborated by most studies that have also observed depression in IBD patients<sup>2,9,10,15,16,21,23</sup>.

Several scoring systems are available to assess disease activity in CD and UC. But despite widespread use, no scores have been confirmed in clinical practice. The gold standard for IBD severity indices does not yet exist. Although somewhat limited by subjective definitions/interpretations, their benefit is in monitoring the clinical course as well as response to therapy<sup>24</sup>.

According to the clinical assessment tool, using the Partial Mayo Index Score and Harvey-Bradshaw Index score, almost 26% of patients in our study suffer from an active form of the disease. Data from prospective studies conducted by Porcelli et al<sup>25</sup> reported disease activity to unequivocally negatively influence IBD patients psychologically. The significant increase in levels of depression and anxiety were a consequence of the disease worsening. Häuser et al<sup>26</sup> has shown IBD patients in remission to have an incidence of mental disorders not substantially different from the general population. Stevens et al<sup>8</sup> have also reported patients in remission after 14 weeks biological therapy to have significantly improved their sleep as well as their symptoms of depression and anxiety.

It is essential to note that a chronic disease, such as CD and UC, may led to a decrease in one's physical fitness and appetite, as well as an increase in fatigue, the development of sleep disorders and other symptoms of depression<sup>27</sup>. As most of these symptoms are included in the questionnaire to screen for depression, it may account for the

**Table II.** Characteristics of the IBD patient sample according to PHQ9 distribution into two groups:  $PHQ9 \ge 10$  and PHQ9 < 10.

Variables	ALL	PHQ9 ≥ 10, n = 18	PHQ9 < 10, n = 72
Age, year, mean ±s d	$41.24 \pm 13.58$	41.72 ± 15.28	41.13 ± 13.23
Gender, n (%)	51 (5(7)	0 (4.4.4)	42 (50.7)
Male	51 (56.7)	8 (44.4)	43 (59.7)
Female	39 (43.3)	10 (55.6)	29 (40.3)
Age, n (%)			
< 60	80 (88.9)	16 (88.9)	64 (88.9)
$\geq 60$	10 (11.1)	2 (11.1)	8 (11.1)
Smoking, n (%)			
Yes	20 (22.2)	6 (33.3)	14 (19.4)
No	70 (77.8)	12 (66.7)	58 (80.6)
In relationship, n (%)			
Yes	57 (63.3)	8 (44.4)	49 (68.1)
No	33 (36.7)	10 (55.6)	23 (31.9)
Employment, n (%)		, ,	,
Yes	58 (64.5)	9 (50)	49 (68.1)
No	32 (35.6)	9 (50)	23 (31.9)
Education, n (%)	()	· ()	()
Elementary	6 (6.7)	1 (5.6)	5 (6.9)
High	64 (71.1)	15 (83.3)	49 (68.1)
Faculty	20 (22.2)	2 (11.1)	18 (25.0)
Socio-economic status, n (%)	20 (22.2)	2 (11.1)	16 (23.0)
	10 (21.1)	5 (27.8)	14 (10 4)
Low	19 (21.1)	5 (27.8)	14 (19.4)
Middle + High	71 (78.9)	13 (72.2)	58 (80.6)
Onset of disease, n (%)	(4 (71.1)	11 ((1.1)	52 (52 6)
$\leq$ 30 years	64 (71.1)	11 (61.1)	53 (73.6)
> 30 years	26 (28.9)	7 (38.9)	19 (26.4)
Disease duration, n (%)			
≤ 5 years	46 (51.1)	11 (61.1)	35 (48.6)
> 5 years	44 (48.9)	7 (38.9)	37 (51.4)
Surgical treatment, n (%)			
Yes	23 (25.6)	2 (11.1)	21 (29.2)
No	67 (74.4)	16 (88.9)	51 (70.8)
Hospitalization in last year, n (%)			
Yes	31 (34.4)	7 (38.9)	24 (33.3)
No	59 (65.6)	11 (61.1)	48 (66.7)
Disease activity, n (%)			
Active disease	23 (25.6)	10 (55.6)	13 (18.1)
Non active disease	67 (74.4)	8 (44.4)	59 (81.9)
Biological therapy, n (%)	,	,	,
Anti TNF	53 (58.9)	10 (55.6)	43 (59.7)
Vedolizumab	37 (41.1)	8 (44.4)	29 (40.3)
Duration of biological therapy, n (%)	37 (11.1)	o ()	25 (10.5)
$\leq 1$ year	11 (12.2)	5 (27.8)	6 (8.3)
> 1 year	79 (87.8)	13 (72.2)	66 (91.7)
IBD, n (%)	17 (01.0)	13 (12.2)	00 (71.1)
UC	48 (53.3)	12 (66.7)	36 (50)
CD		6 (33.3)	36 (50)
Corticosteroids in last year, n (%)	42 (46.7)	0 (33.3)	30 (30)
	21 (22 2)	0 (50)	12 (16.7)
Yes	21 (23.3)	9 (50)	12 (16.7)
No This provides a reflect	69 (76.7)	9 (50)	60 (83.3)
Thiopurine, n (%)	22 (25 ()	9 (4.4.4)	15 (20.9)
Yes	23 (25.6)	8 (44.4)	15 (20.8)
No 51.31	67 (74.4)	10 (55.6)	57 (79.2)
5ASA, n (%)			
Yes	47 (52.2)	12 (66.7)	35 (48.6)
No	43 (47.8)	6 (33.3)	37 (51.4)

PHQ9 - The Patient Health Questionnaire 9, 5 ASA - Aminosalicylates.

**Table III.** Univariate and multivariate logistic regression of the association between IBD patient demographic and disease characteristics and presence of depression according to PHQ9 scoring.

	Univariate		Multivariate	
	Odds ratio (95% CI)	Sig.	Odds ratio (95% CI)	Sig.
Age, years	1.012 (0.984-1.042)	0.384		
Sex (male vs. female)	0.694 (0.316-1.524)	0.363		
$Years < 60 \ vs. \ge 60$	1.035 (0.298-3.586)	0.956		
Smoking (yes vs. no)	1.776 (0.705-4.470)	0.222		
In relationship (yes vs. no)	0.391 (0.173-0.885)	0.024	0.622 (0.258-1.495)	0.289
Employment (yes vs. no)	0.527 (0.234-1.189)	0.123		
Education	0.979 (0.459-2.088)	0.957		
Socio-economic status	1.126 (0.602-2.107)	0.709		
Onset of disease ( $\leq 30 \text{ vs.} > 30$ )	0.455 (0.193-1.071)	0.071		
Disease duration in years ( $\leq 5 \text{ vs.} > 5$ )	1.173 (0.537-2.559)	0.688		
Surgical treatment (yes vs. no)	0.855 (0.348-2.104)	0.735		
Disease activity (yes vs. no)	6.656 (2.576-17.19)	0.000	5.708 (2.138-15.23)	0.001
Hospitalization in last year (yes vs. no)	1.427 (0.631-3.226)	0.393		
Biological therapy (anti TNF vs. vedolizumab	0.778 (0.353-1.714)	0.534		
Duration of biological therapy in years	0.989 (0.965-1.014)	0.405		
Duration of biological therapy ( $\leq 1$ year $vs. > 1$ year)	2.414 (0.757-7.697)	0.136		
IBD (UC vs. CD)	1.221 (0.558-2.672)	0.616		
Corticosteroids in last year (yes vs. no)	4.224 (1.658-10.76)	0.003	2.521 (0.926-6.864)	0.070
Thiopurine (yes vs. no)	2.502 (1.031-6.069)	0.042	2.160 (0.834-5.597)	0.113
5ASA (yes vs. no)	1.165 (0.533-2.543)	0.701		

IBD – inflammatory bowel disease, 5 ASA – Aminosalicylates.

increase in the percentage of 'depressed' patients, especially among those suffering from active IBD disease.

The relationship of one's marital status to symptoms of depression in IBD has here also been investigated. Fuller-Thomson et al<sup>5</sup> have also found depression rates to be higher among IBD patients who are single. This was confirmed by univariant, but not multivariate analysis in our study.

The literature review provides disparate results on the influence of non-biological drugs, corticosteroids and immunosuppressants on symptoms of depression in IBD. The early effects of corticosteroid use in patients are a feeling of well-being, but also mild euphoria or anxiety. The prevalence of depression is greater in patients on more long-standing therapy.

Choi et al<sup>23</sup> have reported depression and anxiety to be more common in patients receiving corticosteroids in the first year after their initial diagnosis. Long et al<sup>28</sup> have also noted a more frequent use of corticosteroids among elderly patients suffering from depression. In contrast, a study conducted by Nohon et al<sup>15</sup> confirms our results found here in which the use of corticosteroids is not associated with excess depression.

The multivariate analysis in our study has yielded results indicating medicating through corticosteroids and thiopurines over the last year is not associated with more severe symptoms of depression in IBD patients receiving biological therapy. However, it must be also noted that the use of corticosteroids in the last year is close in statistical significance.

Ultimately, comparing the results of studies related to risk factors for symptoms of depression in IBD patients is challenging due to several reasons. These include differences in the population from which the study is sampled, the use of diverse drugs in treating IBD, the use of multiple methods (scores) to diagnose depression and the potential risk factors being studied.

This study is potentially limited as was carried out at only one center and therefore it was necessary to include all patients on biological therapy to create a significant sample size. The switch or swap of biological medications during treatment is, therefore, an unwanted but uncontrollable possibility affecting the results of this study. Finally, as the PHQ9 test is a screening test, it does not constitute a conclusive and definitive diagnosis of depression. Hence, in future, psychiatrists should be included in the examination of such a study.

To our knowledge, our study represents the first attempt to investigate the prevalence and predictors of depression with biologic treatment, vedolizumab and anti-TNF agents.

According to our paper, the percentage of patients presenting symptoms of depression does not differ greatly from the general percentage of such patients among the total IBD population. Given that the study included the most severe IBD patients, suffering from an aggressive form of the disease, a higher percentage of symptoms of depression is to be expected. Moreover, as the overall percentage of depressed patients does not differ significantly from the general percentage, can we conclude that biological therapy may reduce symptoms of depression in these patients?

The study unequivocally indicates that in the daily work it is necessary to pay more attention to the mental status of patients, especially those in active disease. Depression tests should be included in daily practice, to identify, monitor and treat such patients in a timely manner.

# Conclusions

Summarily, the above results indicate most of severe symptoms of depression to be present in 20% of the IBD patients examined who are receiving in a venous biological therapy. Timely detection of symptoms of depression is only made possible using screening tests in everyday work. By doing so, patients who need further examination and adequate treatment may be identified. Particular attention and efforts should be focused on patients who have an active form of the disease.

### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

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