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ARTICLE

Prevalence and Factors Associated with Depression, Anxiety and Stress in IBD Patients Undergoing Intravenous Biological Therapy during the COVID-19 Pandemic-Montenegro Experience

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ABSTRACT

Throughout its duration, the coronavirus disease 2019 (COVID-19) pandemic has been affecting lives worldwide and has had a sizeable impact on mental health, particularly for those who already suffer from a chronic illnesses. Depression, Anxiety and Stress (DAS) are common psychiatric comorbidities in inflammatory bowel disease (IBD) patients. This study aims to determine the prevalence and risk factors for moderate and severe symptoms of DAS in IBD patients have been undergoing intravenous biological therapy (IvBTh) during the COVID-19 pandemic. The study was conducted between September 1st and November 30th, 2020 at the Clinical Center of Montenegro-IBD unit, where all patients from Montenegro received the registered IvBTh. This case control study consists of 94 IBD patients that completed a validated questionnaire Depression, Anxiety and Stress Score-21 (DASS-21). A total of 59 patients received tumor necrosis factor alpha inhibitors (anti-TNF therapy), while 35 received anti-integrin therapy. After we calculated the DASS-21 score, we divided the patients into two groups: those who had moderate and severe symptoms (if they had any of the mentioned DASS-21 subscale score above limit for moderate or more severe symptoms: DASS-21 Depression, higher than 14; DASS-21 Anxiety, higher than 10 and DASS-21 Stress, higher than 19) and those who did not have significant symptoms (DASS-21 subscale score did not exceed the limit). We also examined demographic data, data on IBD characteristics and COVID-19 data and their impact on mental disorders. Standard statistical processing tests were used to identify risk factors for examined mental disorders. Following the DASS-21 criteria, we diagnosed the least moderate depression in 19.1%, anxiety in 14.9% and stress in 20.2% patients. The multivariate analysis indicated there to be a statistically significant relation of being higher at risk of developing depression, anxiety and stress when suffering from an active form of IBD (OR 6.487; 95% Cl 1.220–34.500, $P = 0.028$). Almost one third (30.9%) of patients have at least one of the examined mental disorders during the COVID-19 pandemic. Particular attention and efforts must be better focused on patients who suffer from an active form of IBD during the ongoing COVID-19 pandemic.

KEYWORDS

Inflammatory bowel disease; depression; anxiety; stress; COVID-19

1 Introduction

The coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2). Since March 12th, 2020, the World Health Organization has declared a global pandemic of the COVID-19 [1]. The COVID-19 pandemic has been having an overtly negative impact on physical as well as mental health worldwide [1,2]. Relatively high rates symptoms of depression (14.6% to 48.3%), anxiety (6.33% to 50.9%) and stress (8.1% to 81.9%) have been documented among the general population in countries facing a high prevalence of COVID-19, such as China, Italy, Spain, Iran, the US, Turkey, Nepal and Denmark [3–6]. There are a number of sociodemographic variables associated with high levels of Depression, Anxiety and Stress (DAS) in relation to COVID-19. Some of them are gender, age of patients, if one is unemployed, knowing someone who has been infected, suffering from a negative affect or detachment, the presence of chronic/psychiatric illnesses, being frequently exposed to social media/news concerning COVID-19, having a history of past trauma or stress as well as already suffering from existing medical problems [3–6].

On the other hand, independent of the COVID-19 pandemic, psychiatric conditions such as anxiety and depression are significantly more common in IBD patients than the general population [7]. There is a higher risk of developing one of these disorders within the first year following the initial diagnosis of IBD [7]. Addolorato et al. [8] have reported that more than 80% of active-disease IBD patients suffered from anxiety and approximately 60% from concomitant depression. The results of our previously published study in IBD patients on Intravenous Biologic Therapy (IvBTh) showed that 20% of patients had significant depressive symptoms [9]. Other studies have shown that biological therapy may help to reduce symptoms of depression in IBD patients [10,11].

It has been shown that IBD patients have a more severe fear of contracting COVID-19 than the general population [1]. However, IBD patients do not appear to be at higher risk from COVID-19 infection of than the general population [12]. Treatment of COVID-19 while also using biologics and immunomodulators is not associated with a worse prognosis [12–14], although systemic steroids are suspected to be potentially detrimental [12,13,15].

1.1 What Is the Impact of the COVID-19 Pandemic on Mental Disorders in IBD Patients? What Data Do We Have So far?

Cheema et al. [3] have documented high rates of depression (34.9%), anxiety (32.0%) and stress (29.7%) among IBD without a pre-existing diagnosis of anxiety or depression during the COVID-19 pandemic. Significant predictors are reported to be if one is younger, suffers from an active form of the disease, lacks access to an IBD nurse and is not given sufficient advice from a medical practitioner [3].

According to the data available, the COVID-19 pandemic has had a high impact on the mental health of the overall general population, including patients who already suffer from IBD that may already have an adverse effect on their quality of life [3,16–18].

Our country, in the second half of 2020, had a high incidence of COVID-19 infection, one of the largest in Europe at the time. In this context, we wanted to examine the impact of the COVID-19 pandemic on the mental health of IBD patients. We wanted to determine the frequency of mental disorders in those patients with the most aggressive course of the disease. Therefore, we would choose patients on IvBTh for the study. Since, all patients with IBD from Montenegro receive registered intravenous biological therapy at the Clinical Center of Montenegro and thus would have a total prevalence of these patients in our country. Moreover, to the best of our knowledge, there is no published research or study about the impact of the COVID-19 pandemic on mental health of IBD patients receiving IvBTh.

Examining the mental status of IBD patients treated with IvBTh during the COVID-19 pandemic, we can identify the most significant factors that may be related to these disorders. In this way, we will select

patients who need psychological support and/or psychiatric treatment. In this study, we want to examine the impact of the COVID-19 pandemic on the number of patients with depressive symptoms compared to our pre-pandemic study [9].

The aim of this study, therefore, is to determine the prevalence and risk factors for at least moderate symptoms of DAS in IBD patients have been undergoing IvBTh during the COVID-19 pandemic in Montenegro. Also, in this way we would select patients with mental disorders earlier and increase their quality of life.

2 Material and Methods

The case control study was conducted between September 1st and November 30th, 2020 at the Clinical Center of Montenegro-IBD unit, where all patients from Montenegro received the registered IvBTh. This study was comprised of patients older than 18 years of age, with a pathohistologically confirmed diagnosis of IBD (Ulcerative Colitis–UC, and Crohn's Disease–CD). All patients (94) were suffering from an aggressive form of the disease and had been receiving IvBTh (anti TNFα: infliximab-originator and biosimilar (59 patients) and anti-integrins: vedolizumab (35 patients)) for at least 6 months prior). Similar frequency of UC and CD, 42 patients (44.7%) had CD, and 52 (55.3%) were diagnosed with UC.

During regular admission to biological therapy at the IBD unit, the patients were administered the validated questionnaire "Depression, Anxiety, Stress Score-21" (DASS-21). The survey was anonymous and personal data were not collected. Quick and direct for patients to complete, the validated questionnaire DASS-21 itself is a tool for healthcare professionals to diagnose mental health disorders [3,19]. A simple test, containing 21 items with 7 items per its subscale domain: depression, anxiety and stress. Respondents score all items from 0 to 3, whose total scores are added together and multiplied by 2 for each domain to generate three subscale scores [19]. All three of the subscale scores (DASS-21 Depression, DASS-21 Anxiety, DASS-21 Stress) are graded into four subgroups (normal, mild, moderate and severe). Depression subscale scores (DASS-21 Depression) correspond to normal population (0–9), mild (10–13), moderate (14–20) and severe symptoms (21–27). Anxiety subscale scores (DASS-21 Anxiety) correspond to normal population (0–7) mild, (8–9) moderate (10–14) and severe symptoms (15–19). Stress subscale scores (DASS-21 Stress) correspond to normal population (0–14), mild (15–18), moderate (19–25) or severe symptoms (26–33) [19]. As significant symptoms on the DASS-21 score in our study, we marked if it was at least a moderate DASS-21 subscale score (at least moderate DAS): DASS-21 Depression (higher than 14), DASS-21 Anxiety (higher than 10) and DASS-21 Stress (higher than 19). According to these, we divided the patients into two groups: those who had significant symptoms on the DASS-21 score (if they had any of the mentioned DASS-21 subscale score above limit) and those who did not have significant symptoms (DASS-21 subscale score did not exceed the limit).

The Simple Clinical Colitis Activity Index (SCCAI) was used to assess the disease activity of Ulcerative Colitis (UC); for Crohn's Disease (CD), the Harvey-Bradshaw Index (HBI) was used [20,21]. An active form of the disease (moderate and severe) for UC was defined as a SCCAI equal to or greater than 5 for CD (moderate and severe) and an HBI equal to or greater than 8.

We also collected data on patients' demographics (personal and social habits, marital and socio-economic status, status of employment) and data on IBD characteristics and course of disease (IBD type, duration of disease, disease activity, previous treatment, other medical history). Also, COVID-19 data such as patient's general knowledge about COVID-19 virus, their health concerns during the COVID-19 pandemic about the outcome of a possible infection and patients' behaviour data and social distancing. Patients were asked about persistent of the symptoms that corresponded to the symptoms of COVID-19 infection (dry cough, headache, weakness, diarrhoea, fever) in the last two weeks. At the time of the study, there were no patients who were vaccinated and SARS CoV2 positive.

Exclusion criteria: The study excluded all patients who had already been mental illnesses and who regularly used antidepressants and/or anxiolytics, as well as patients who had already been infected by COVID-19. Patients expressing any refusal in participating in the study along with any who were unable to complete the questionnaires on their own were also excluded from the study.

IBM SPSS Statistics for Windows, Version 22.0 was used to carry out the statistical analyses. Percentages, means and variability measures (interquartile range-IQR) are the descriptive statistical methods applied. Among the analytical statistical methods applied were confidence intervals (for OR), the Pearson's Chi-squared test, as well as univariate and multivariate binary logistic regression. The dependent variables were "moderate to severe DAS", where in all independent variables from the general questionnaire might relate to the dependent variables.

We first analysed the correlation of each of the independent variables separately against those dependent through the Chi-squared test. For those variables where the Chi-squared test showed a statistical significance, a univariate logistic regression model was applied to determine the OR (odds ratio) and a 95% confidence interval for OR. These variables were then included in a multivariate binary logistic regression model to discover which of these variables correlate most with "at least moderate DAS". A P value < 0.05 was considered to be statistically significant.

3 Results

This study included 54 (57.4%) males and 40 (42.6%) females. The median value for the patients' age was 38.0 (IQR 30–54) years. Based on the scores of IBD activity, 15 patients (16.0%) had an active form of disease, 10 UC patients (19.2%) and 5 CD patients (11.9%). Other demographic data (personal and social habits, marital and socio-economic status, employment status), data related to IBD course (onset/duration of disease, exacerbation and need for hospital treatment in last year), type of IvBTh and previous treatment are summarized in Table 1.

Table 1: Characteristics of our IBD patients according to DASS-21 score

Variables	All		Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	P value
	n	%						
Gender, n (%)							χ^2	
Female	40	42.6	14	35.0	26	65.0	0.562	0.503
Male	54	57.4	15	27.8	39	72.2		
Smoking, n (%)								
Yes	13	13.8	5	38.5	8	61.5	0.410	0.748
No	81	86.2	24	29.6	57	70.4		
In relationship, n (%)							χ^2	
Yes	65	69.1	21	32.3	44	67.7	0.210	0.647
No	29	30.9	8	27.6	21	72.4		
Employment, n (%)							χ^2	
Yes	45	47.9	12	26.7	33	73.3	0.709	0.400
No	49	52.1	17	34.7	32	65.3		

(Continued)

Table 1 (continued)

Variables	All n	%	Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	*P* value
Education, n (%)							χ^2	
High school	57	60.6	18	31.6	39	68.4	0.036	0.850
Faculty	37	39.4	11	29.7	26	70.3		
Socio-economic status, n (%)							χ^2	
Low	9	9.6	6	66.7	3	33.3	5.985	0.023
Middle + High	85	90.4	23	27.1	62	72.9		
Family members, n (%)							χ^2	
≥3	65	69.1	21	32.3	44	67.7	0.210	0.642
<3	29	30.9	8	27.6	21	72.4		
IBD characteristics and course								
Type of IBD, n (%)							χ^2	
Crohn's disease	42	44.7	15	35.7	27	64.3	0.842	0.359
Ulcerative colitis	52	55.3	14	26.9	38	73.1		
Disease duration, n (%)							χ^2	
>5 years	46	48.9	19	41.3	27	58.7	4.614	0.032
≤5 years	48	51.1	10	20.8	38	79.2		
Disease activity, n (%)							χ^2	
Active disease	15	16.0	9	60.0	6	40.0	7.109	0.013
Non active disease	79	84.0	20	25.3	59	74.7		
Hospitalization in the last year, n (%)							χ^2	
Yes	19	20.2	6	31.6	13	68.4	0.006	0.939
No	75	79.8	23	30.7	52	69.3		
Exacerbation of the disease over the previous year, n (%)							χ^2	
Yes	36	38.3	12	33.3	24	66.7	0.169	0.681
No	58	61.7	17	29.3	41	70.7		
Biological and conventional drugs								
Biological therapy, n (%)								
Anti TNF	59	62.8	18	30.5	41	69.5	0.009	0.926
Vedolizumab	35	37.2	11	31.4	24	68.6		
Thiopurine in last year, n (%)							χ^2	
Yes	21	22.3	8	38.1	13	61.9	0.665	0.415
No	73	77.7	21	28.8	52	71.2		

(Continued)

Table 1 (continued)

Variables	All n	%	Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	*P* value
Corticosteroids in last year, n (%)							χ^2	
Yes	23	24.5	6	26.1	17	73.9	0.324	0.569
No	71	75.5	23	32.4	48	67.6		

Note: χ2-Pearson's Chi-squared test, IBD–inflammatory bowel disease, DASS-21-Questionnaire for Depression, Anxiety and Stress, Significant symptoms on DASS-21 score-at least moderate results for Depression and/or Anxiety and/or Stress.

About almost three quarters of patients in our study reported that they considered themselves to be well-informed about COVID-19. Our patients reported that in the immediate vicinity, there were 22 (23.4%) positive individuals for SARS-CoV-2 and 40 (42.6%) individuals in quarantine isolation (Table 2).

Table 2: Data collected about COVID-19 from IBD patients, sample according to DASS-21 score

Variables	All n	%	Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	*P* value
Knowledge about COVID-19, n (%)							χ^2	
Bad	2	2.1	0	0	2	100	2.939	0.600
Satisfactory	23	24.5	5	21.7	18	78.3		
Good	43	45.7	16	37.2	27	62.8		
Very good	21	22.3	7	33.3	14	66.7		
Excellent	5	5.3	1	20.0	4	80.0		
Positive cases COVID-19 (in the immediate vicinity), n (%)							χ^2	
Yes	22	23.4	10	45.5	12	54.5	2.871	0.090
No	72	76.6	19	26.4	53	73.6		
Quarantine isolation (person from the immediate vicinity), n (%)							χ^2	
Yes	40	42.6	14	35.0	26	65.0	0.562	0.454
No	54	57.4	15	27.8	39	72.2		
Health concerns during COVID 19 pandemic								
Concerns about coming to the IBD unit to be administered their biological therapy during the COVID-19 pandemic, n (%)							χ^2	
Moderate to very concern	44	46.8	19	43.2	25	56.8	5.896	0.015
Not et all or only occasionally somewhat concern	50	53.2	10	20.0	40	80.0		

(Continued)

Table 2 (continued)

Variables	All n	%	Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	*P* value
Health concerns during the first COVID-19 wave, n (%)							$\chi 2$	
Moderate to very concern	66	70.2	27	40.9	39	59.1	9.096	0.003
Not et all or only occasionally somewhat concern	28	29.8	2	7.1	26	92.9		
Health concerns during the second COVID-19 wave, n (%)							$\chi 2$	
Moderate to very concern	60	63.8	25	41.7	35	58.3	10.507	0.001
Not et all or only occasionally somewhat concern	34	36.2	4	11.8	30	88.2		
Patients' symptoms, similar to the most common symptoms of COVID 19								
Fever (In the last two weeks), n (%)							$\chi 2$	
Yes	9	9.6	4	44.4	5	55.6	0.862	0.353
No	85	90.4	25	29.4	60	70.6		
Headache (In the last two weeks), n (%)							$\chi 2$	
Yes	25	26.6	13	52.0	12	48.0	7.141	0.008
No	69	73.4	16	23.2	53	76.8		
Muscle pain (In the last two weeks), n (%)							$\chi 2$	
Yes	11	11.7	7	63.6	4	36.4	6.277	0.018
No	83	88.3	22	26.5	61	73.5		
Dry cough (In the last two weeks), n (%)							$\chi 2$	
Yes	5	5.3	4	80.0	1	20.0	5.980	0.03
No	89	94.7	25	28.1	64	71.9		
Fatigue (In the last two weeks), n (%)							$\chi 2$	
Yes	12	12.8	8	66.7	4	33.3	8.271	0.007
No	82	87.2	21	25.6	61	74.4		
Diarrhoea (In the last two weeks), n (%)							$\chi 2$	
Yes	22	23.4	11	50.0	11	50.0	4.937	0.026
No	72	76.6	18	25.0	54	75.0		
Social distance								
I try to be isolate every day (In the last two weeks), n (%)							$\chi 2$	
More than 10 h	26	27.7	11	42.3	15	57.7	3.564	0.168
8–10 h	37	39.4	12	32.4	25	67.6		
Less than 8	31	32.9	6	19.4	25	80.6		

(Continued)

Table 2 (continued)

Variables	All n	%	Significant symptoms on DASS-21 score		Non-significant symptoms on DASS-21 score		Statistic test	*P* value
I have been avoiding places with more people, (In the last two weeks), n (%)							χ^2	
Yes	87	92.6	26	29.9	61	70.1	0.511	0.672
No	7	7.4	3	42.9	4	57.1		
I have been avoiding lately handling, (In the last two weeks), n (%)							χ^2	
Yes	85	90.4	27	31.8	58	68.2	0.347	0.716
No	9	9.6	2	22.2	7	77.8		
I have been avoiding lately contacts with other people, (In the last two weeks), n (%)							χ^2	
Yes	80	85.1	26	32.5	54	67.5	0.685	0.538
No	14	14.9	3	21.4	11	78.6		

Note: χ2-Pearson's Chi-squared test, IBD–inflammatory bowel disease, DASS-21-Questionnaire for Depression, Anxiety and Stress, Significant symptoms on DASS-21 score-at least moderate results for Depression and/or Anxiety and/or Stress.

Slightly more than half of all patients (53.2%) reported that they were either not at all or only occasionally somewhat concerned about coming to the IBD unit to receive biologic therapy during the COVID-19 pandemic. These results, as a data related to our patients' knowledge of COVID-19, patients' symptoms-similar to the most common symptoms of COVID-19, behavioural-social distance are shown in Table 2.

Following the DASS-21 criteria, 18 patients (19.1%) of all respondents were at least moderately depressed, 14 patients (14.9%) had anxiety and 19 patients (20.2%) stress. The percentage of patients who met the criteria for at least moderate symptoms on DASS-21 score for at least one of the disorders was 29 patients (30.9%), almost a third.

The predictors for at least moderate DAS were statistically significant on a multivariate analysis that included only disease activity (OR 6.487; 95% Cl 1.220–34.500, $P = 0.028$). This and other results of the univariate and multivariate analyses for the risk factors for at least moderate DAS in IBD patients undergoing IvBTh during the COVID-19 pandemic are given in Table 3.

Table 3: Risk factors on univariate and multivariate logistic regression for at least moderate depression, anxiety and stress according to DASS-21 scoring during COVID-19 pandemic

	Univariate		Multivariate	
	Odds ratio (95% CI)	Sig.	Odds ratio (95% CI)	Sig.
Demographic and IBD characteristics				
Socio-economic status Low *vs.* Middle/ High	5.391 (1.244–23.359)	0.024	2.796 (0.412–18.958)	0.292

(Continued)

Table 3 (continued)

	Univariate		Multivariate	
	Odds ratio (95% CI)	Sig.	Odds ratio (95% CI)	Sig.
Disease duration in years (≤5 *vs.* >5)	2.674 (1.075–6.649)	0.034	1.952 (0.618–6.160)	0.254
Disease activity (In the last two weeks) Yes *vs.* No	4.425 (1.400–13.986)	0.011	6.487 (1.220–34.500)	0.028
Health concerns during COVID-19 pandemic				
Concerns about coming to IBD unit to be administered their biological therapy during the COVID-19 pandemic	3.040 (1.218–7.585)	0.017	1.833 (0.519–6.473)	0.346
Moderate to very concern *vs.* Not et all or only occasionally somewhat concern				
Health concerns during the first COVID-19 wave	9.000 (1.969–41.135)	0.005	4.680 (0.607–36.091)	0.139
Moderate to very concern *vs.* Not et all or only occasionally somewhat concern				
Health concerns during the second COVID-19 wave	5.357 (1.675–17.135)	0.005	1.610 (0.270–9.615)	0.601
Moderate to very concern *vs.* Not et all or only occasionally somewhat concern				
Patients' symptoms, similar to the most common symptoms of COVID-19				
Headache (In the last two weeks) Yes *vs.* No	3.589 (1.369–9.404)	0.009	3.032 (0.794–11.571)	0.105
Muscle pain (In the last two weeks) Yes *vs.* No	4.852 (1.294–18.194)	0.019	0.457 (0.054–3.842)	0.471
Dry cough (In the last two weeks) Yes *vs.* No	10.240 (1.091–96.143)	0.042	5.593 (0.187–167.426)	0.321
Fatigue (In the last two weeks) Yes *vs.* No	5.810 (1.585–21.288)	0.008	7.568 (0.795–72.027)	0.078
Diarrhea (In the last two weeks) Yes *vs.* No	3.000 (1.113–8.086)	0.030	1.470 (0.350–6.163)	0.599

Note: IBD–inflammatory bowel disease.

4 Discussion

Patients with IBD are more vulnerable to psychological stress than the general population. The impact of the COVID-19 pandemic on the mental health of patients with IBD is still insufficiently studied and poorly understood.

There are few papers in the literature addressing the prevalence and risk factors for depression, anxiety and stress in IBD patients during a pandemic.

Our study has found a prevalence for moderate or more severe symptoms of depression (19.1%), anxiety (14.9%) and stress (20.2%) in IBD patients undergoing IvBTh during the COVID-19 pandemic. These results also showed the overall prevalence of the examined mental disorders in IBD patients undergoing

IvBTh in our country, for the period in which the study was conducted. As almost one third (30.9%) of patients have at least one of the mental disorders examined during the COVID-19 pandemic, we must make new efforts to improve the prevention of these conditions, early detection, to provide adequate psychological assistance to all who need it.

However, these results suggest a lower prevalence of the examined mental disorders compared to other studies. In the study, Cheema et al. have a much higher percentage of patients who had symptoms of moderate to severe DAS (34.9%, 32.0% and 29.7%, respectively) [3]. Also, Mosli et al. [22] have reported that 48.4% of respondents expressed symptoms of anxiety, but the participant scores were not consistent with depression. A possible explanation for the results is that our study included fewer patients than these studies [3,22], especially compared to the study by Mosli et al. [22], which used a different scale to assess depression and anxiety, also.

Interpretation of results should be carefully considered having in mind disparity between studies because of patients clinical and socio-epidemiological heterogeneity. Heterogeneity among patients is a consequence of different ages, disease stages and activities, treatment, socioeconomic status of patients and different approaches to mental illness in different countries.

As the study has included the most severe IBD patients suffering from an aggressive form of the disease during the height of the COVID-19 pandemic, a higher percentage symptoms of DAS is to be expected. The effect of biological therapy on depression has been investigated in numerous studies, widely finding that medication for IBD, including immunomodulatory and anti-TNF therapy, significantly improves symptoms of depression [10,11]. The anti-TNF and immunomodulation therapy significantly decreased the number of patients who met criteria for at least moderate depression after treatment for 1–6 months [11]. Stevens et al. [10] study showed that not only anti-TNF biologic therapy but also vedolizumab were associated with improved sleep quality and mood in IBD. Ultimately, it may be concluded that the regular application of biological therapy may potentially reduce symptoms of DAS, especially if an enhanced inflammatory response may be brought under control in the patient.

Although DAS symptoms are common among IBD patients during a pandemic, when compared to pre-pandemic study results, they are different. Some studies show a higher prevalence for depression (from 24% to 25.8%) [18,23], for anxiety (from 21.2% to 44%) [18,23] or for anxiety/depression (up to 30.3%) [24] in IBD patients. There are also studies that have described much lower percentages of depression (8.0%) and anxiety (12.2%) in IBD patients before the COVID-19 pandemic [25].

Interestingly, the prevalence of depression of 19.1% in this study is similar to the rates in our pre-pandemic study, where 20% of patients with IBD on IvBTh met the criteria for the least moderate symptoms of depression [9]. It is possible to speculate that the COVID-19 pandemic did not affect the incidence of depression in our IBD patients. However, the percentage of active-disease patients in our study was found to be substantially lower (16%) to that of the study conducted prior to the pandemic (25.6%) [9]. The reason for the similar prevalence of depression in both studies can be explained by the higher percentage of patients with active disease in the pre-pandemic study, which would mean that the COVID-19 pandemic increased the prevalence of depression among those who did not have active IBD during the pandemic. This would mean that the mental health of patients without active IBD during the COVID-19 pandemic should also be assessed.

Considering even the above, our study proved that the main predictor of at least moderate DAS is IBD disease activity. Several scoring systems are available to assess disease activity in CD and UC. The gold standard for IBD severity indices does not yet exist. According to clinical assessment tools, using the results of SCCAI and HBI, 16% of patients in our study suffer from the active form of their disease, as we mentioned earlier. It is known that active disease is associated with psychological morbidity [26]. Multivariate statistical analysis of our study indicated active disease as the most significant and only risk

factor in the development of symptoms of least moderate DAS. Patients with active IBD were about 6.5 times more likely to develop DAS. When summarizing the results of this and a pre-COVID study [9], a pandemic could affect the symptoms of depression in people without active IBD. We can expect different mental disorders in a patient with active IBD, even when receiving biologic therapy.

The same conclusion has also been reported by the majority of studies also observing DAS symptoms in IBD patients [8,18,24,25,27,28]. It can be assumed that active IBD disease leading to mental disorders will certainly affect the quality of life of patients. As reported from the first prospective, long-term follow-up study conducted by Mittermaier et al. on IBD patients in remission after a flare-up, depression and anxiety likely indicate poor quality of life and potentially are risk factors for early clinical recurrence [29]. Data from prospective studies conducted by Porcelli et al. [30] reported poor quality of life as well as disease activity to unequivocally negatively influence IBD patients psychologically [31]. Therefore, it is commonly proposed that IBD patients seek mental health counselling in some form [32].

Contrary to these findings, though, Kim et al. [23] reported a high prevalence of DAS symptoms despite clinical remission in Korean IBD patients. Azzam et al. [33] though, report quality of life and disability to be unaffected by the COVID-19 pandemic (77.97% of their participants were on biologics). More studies are needed to examine the impact of disease activity on the development of mental disorders in the COVID-19 pandemic with a focus on quality of life. This is also in the further focus of our research. Based on our study, we can advise that patients with active IBD should undergo earlier and more frequent mental health monitoring in order to improve their quality of life.

We also analysed the impact of IBD disease duration on the development of mental disorders in the COVID-19 pandemic. Our study showed a statistically significantly higher number of patients with at least moderate DAS symptoms were in the group suffering from IBD for more than 5 years. However, multivariate analysis has not shown that disease duration does have a significant statistical prediction for the least moderate DAS. To date, the literature has not found disease duration to be significantly associated with depression and anxiety [16,18]. Contrary, a study conducted by Kim et al. [23] has found disease duration and socio-economic deprivation to be associated with depression.

Nearly three-quarters of patients in our study said they thought they were well informed about COVID-19. They were concerned about their health during the first and second waves of COVID-19, 70.2% and 63.8%, respectively. The same results reported in studies elsewhere, patients with IBD express greater fear of COVID-19 infection [1,3]. About half of our patients (46.8%) stated that they were moderate or very worried about coming to the IBD ward for biological therapy during the COVID-19 pandemic. Our patients were worried about their health, but with the advice and support of doctors, they came to receive biological therapy. It can be pointed out that over 80% of our patients adhered to the rules of social distance and avoided places with more people.

We investigated the influence of risk factors for SARS CoV2 infection on the occurrence of DAS symptoms in IBD patients. The risk factors we studied were the immediate vicinity with COVID-19 patients and immediate vicinity with persons in quarantine isolation. We did not obtain statistical significance, and we can conclude that these risk factors did not affect the development of DAS. Contrary to our results, Ding et al. had reported that greater personal COVID-19 exposure was significantly associated with increased symptoms of anxiety and depression while country level COVID-19 risk factors were not [34].

By univariate analysis, we showed that the existence of COVID-19-like symptoms (i.e., headache, muscle pain, dry cough, fatigue and diarrhoea) influenced the prediction of DAS, with statistical significance. However, multivariate analysis did not confirm this. In interpreting these results, we must take into account that symptoms such as diarrhoea, headache and fatigue may also be symptoms of active IBD.

Strength

We have pre-COVID-19 psychological data from same cohort, we can comment on the specific effect of the pandemic on their depression, but not on anxiety and stress. The results showed that the pandemic can affect the onset of depressive symptoms in patients who did not suffer from the active form of IBD. This reminds us to pay more attention on IBD management with mental disorders especially depression.

4.1 Limitation

It is true that the study included patients on IvBTh, but not other patients on biological therapy, those receiving subcutaneous biological therapy. Therefore, it is necessary to include all centres that provide biological therapy in IBD patients to create a significant sample size. We do not have matched general population control group, no conclusions can be drawn about the state of mental disorders from IBD in relation to the general population. Moreover, another limitation is derived from the DASS-21. As it is a screening test, it does not constitute a conclusive and definitive diagnosis of DAS. Hence, in future, psychiatrists should be included in any such or similar study.

5 Conclusion

This study has found that almost one third of IBD patients have at least one of the examined mental disorders: depression, anxiety and stress during the COVID-19 pandemic. Special attention should be focused on patients who have an active form of the disease. The study indicates that screening tests for depression, anxiety and stress should be included in daily practice, especially during COVID-19 pandemic, in order to identify IBD patients who may be at an increased risk of either suffering from or developing mental disorders.

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