

DEPRESSION AND ANXIETY
IN IRRITABLE BOWEL SYNDROME
COMPARED WITH INFLAMMATORY BOWEL
DISEASE AND CLOSTRIDIODES DIFFICILE
INFECTION DURING THE COVID-19 PANDEMIC

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Summary

Anxiety and depressive disorders are the most common psychiatric comorbidities in irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and have more than three-fold increased odds compared to healthy subjects. The COVID-19 pandemic affects significant psycho-emotional state in general population. The aim of the study was to evaluate the grade of anxiety and depression in patients with IBS, IBD and those with Clostridioides difficile infection (CDI) during the Covid-19 pandemic. The State-Trait Anxiety Inventory and Hamilton Depression Rating Scale were used to assess anxiety and depression respectively. A total of 30 IBS, 30 IBD and 30 CDI patients were randomly enrolled in this study. Depression was significantly more common in the IBS and CDI groups than in the IBD group (86.7%, 86.7% and 56.7% respectively, $p=0,007$). All patients of all study groups had both subtypes of anxiety of varying degrees. Severe state anxiety was found slightly more frequent in the IBS group than in the IBD and CDI groups (60.0%, 46.7% and 36.7%, respectively; $p=0,192$). Trait anxiety was even more frequent and severe than state anxiety. In conclusion, the level of depression and anxiety becomes extremely high in patients with IBS, IBD and CDI in stressful threatening social conditions, and these patients require appropriate diagnosis and treatment.

Keywords: depression, anxiety, irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Clostridioides difficile, Covid-19

Rezumat

Depresia și anxietatea la pacienții cu sindromul intestinului iritabil în comparație cu bolile inflamatorii intestinale și infecția cu Clostridioides difficile în perioadă de pandemie de COVID-19

Tulburările de anxietate și depresia sunt cele mai frecvente comorbidități psihiatrice în sindromul intestinului iritabil (SII), bolile inflamatorii intestinale (BII) și au o frecvență de peste trei ori mai mare în comparație cu subiecții sănătoși. Pandemia de COVID-19 a afectat semnificativ starea psihemoțională a populației generale. Scopul acestui studiu a fost de a evalua gradul de anxietate și depresie la pacienții cu SII, BII și infecție cu Clostridioides difficile (ICD) în timpul pandemiei de COVID-19. Pentru evaluarea anxietății și, respectiv, a depresiei, s-au utilizat Scala Spielberger care include analiza anxietății reactive și anxietății de personalitate și Scala Hamilton. Pentru a participa la acest studiu, au fost selectați aleatoriu 30 de pacienți cu SII, 30 cu BII și 30 cu ICD. Rezultatele au relevat o prevalență semnificativ mai mare a depresiei în grupurile SII și ICD, comparativ cu grupul BII (86,7%, 86,7% și respectiv 56,7%, $p=0,007$). Toți pacienții din cele trei grupuri de studiu au manifestat ambele subtipuri de anxietate de diferite grade. Anxietatea reactivă severă a fost găsită puțin mai frecventă în grupul

SII decât în grupurile BII și ICD (60,0%, 46,7% și, respectiv, 36,7%; $p=0,192$). Anxietatea de personalitate a fost chiar mai frecventă și mai pronunțată decât anxietatea reactivă. În concluzie, nivelul de depresie și de anxietate devine extrem de ridicat la pacienții cu SII, BII și ICD într-un mediu social stresant și amenințător, iar acești pacienți necesită un diagnostic și tratament adecvat.

Cuvinte-cheie: depresie, anxietate, sindrom de intestin iritabil, boli inflamatorii intestinale, colita ulcerative, boala Crohn, Clostridioides difficile, COVID-19

Резюме

Депрессия и тревожность при синдроме раздраженного кишечника в сравнении с воспалительными заболеваниями кишечника и инфекцией Clostridioides difficile во время пандемии COVID-19

Тревожные и депрессивные расстройства являются наиболее частыми сопутствующими заболеваниями при синдроме раздраженного кишечника (СРК) и воспалительных заболеваниях кишечника (ВЗК). Вероятность их развития у таких пациентов превышает почти в три раза вероятность у здоровых людей. Пандемия COVID-19 существенно повлияла на психоэмоциональное состояние населения в целом. Цель исследования состояла в том, чтобы оценить степень тревожности и депрессии у пациентов с СРК, ВЗК, а также с инфекцией Clostridioides difficile (ИКД) во время пандемии COVID-19. Для измерения уровня тревожности и депрессии использовались шкала тревожности Спилбергера и шкала депрессии Гамильтона соответственно. Общее количество участников исследования составило 30 пациентов с СРК, 30 - с ВЗК и 30 - с ИКД. Депрессия достоверно чаще встречалась в группах СРК и ИКД, чем в группе ВЗК (86,7%, 86,7% и 56,7% соответственно, $p=0,007$). У всех пациентов во всех исследуемых группах диагностировали оба вида тревожности в разной степени. Тяжелая ситуационная тревожность была наблюдаема несколько чаще в группе с СРК, чем в группах с ВЗК и ИКД (60,0%, 46,7% и 36,7% соответственно; $p=0,192$). Личностная тревожность, связанная с индивидуальными чертами характера, оказалась более распространенной и выраженной, чем ситуационная тревожность. Таким образом, уровень депрессии и тревожности сильно возрастает у больных с СРК, ВЗК и ИКД в условиях стресса и социальной напряженности, что подчеркивает необходимость соответствующей диагностики и лечения.

Ключевые слова: депрессия, тревожность, синдром раздраженного кишечника, воспалительные заболевания кишечника, язвенный колит, болезнь Крона, Clostridioides difficile, COVID-19

Introduction

The close relationship between the psycho-emotional state and intestinal disorders has been known for centuries. This relationship can be traced both in healthy individuals and in various intestinal diseases and is probably the most significant and best studied in disorders of the gut-brain interaction (DGBI). DGBI are extremely frequent, worldwide spread disorders that can affect any person, regardless of age, gender, socioeconomic status or other factors [1]. IBS is one of the DGBI, in which abdominal pain is the main symptom, associated with an abnormal number and/or quality of stool. The prevalence of IBS varies by geographic and socioeconomic regions, with an average of 10-20% and is higher among women and young adults. The influence of psycho-emotional factors on IBS is so obvious that for a long time the symptoms of this disorder were perceived as manifestations of a psychological/psychiatric disease. Even the corresponding name was used – “intestinal neurosis”. The understanding of the pathogenesis of these disorders has changed significantly over the past decades, but the modern name – “disorders of gut-brain interaction”, nevertheless also reflects this direct link.

IBS is associated with psychological disorders, more psychiatric distress, sleep disturbance, and others. In addition, IBS is characterized by psychiatric comorbidity. Numerous studies and their meta-analyses have shown that anxiety disorders are the most common psychiatric comorbidity ($\approx 30\%$ of patients), followed by depressive disorders ($\approx 25\%$), and that patients with IBS have a three-fold increased odds of either anxiety or depression, compared to healthy subjects [2, 3].

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are characterized as lifelong disorders with various intestinal and extraintestinal manifestations. Pain syndrome, indigestion, diarrhea and other symptoms cause restrictions in nutrition, in personal and social life of patients and, as a result, a decreased quality of life. Patients with IBD have a significant psychological burden associated with their physical condition and socioeconomic status. Anxiety and depression are the most common psychiatric disorders in patients with IBD, as well as in patients with IBS. The meta-analysis of 171 articles with a total of 158,371 participants indicated that patients with IBD have about a 20% prevalence rate of anxiety and a 15% prevalence rate of depression [4]. A later meta-analysis showed even higher levels, with about one in three patients with IBD diagnosed with symptoms of anxiety and one in four with symptoms of depression [5].

Clostridioides difficile is an anaerobic gram-positive spore-forming bacterium that has become an important human pathogen in recent decades. It produces toxins that provoke a wide range of

intestinal disorders from mild diarrhea to severe forms of fulminant pseudomembranous colitis. The influence of CDI on the functions of the central nervous system has been studied much less. This is due to the fact that, firstly, CDI is a relatively new disease, and, secondly, CDI in most cases has an acute course and only in a number of cases leads to a recurrent evolution. Few studies point to a possible association of microbiota disorders with an overrepresentation of *Clostridioides* species in the pathogenesis of such diseases as autism, Parkinson's disease, Alzheimer's disease [6, 7]. The relationship between anxiety, depression and CDI has been little studied. Single works are devoted to this topic. One such population-based study in the US found that adults with depression, taking antidepressants were more likely to develop CDI [8].

An outbreak of CDI was registered in Moldova in 2020-2021, probably due to COVID-19 infection and concomitant antibiotic therapy. Clinical observation made it possible to suspect a very high frequency of affective disorders in these patients. The conducted pilot study confirmed the presence of depression in an extremely large number of patients with CDI after COVID-19 (24 patients out of 28) [9].

Lockdowns, quarantine measures, and social distancing during the pandemic have had a negative impact on mental health. Moreover, this influence had a direct correlation: higher restrictions due to lockdown measures, a greater reduction of social contacts, and greater perceived changes in life were associated with higher mental health impairments [10]. One of the first works in this area, carried out in Hong Kong showed that “compared with 2016 and 2017, the stress level increased by 28.3%, prevalence of anxiety increased by 42.3%, and the depression symptoms and unhappiness have doubled” during the COVID-19 outbreak [11]. The authors called this significant increase a “mental health crisis” amid the COVID-19 pandemic. Similar data were obtained in the study from Brazil. Moderate-to-severe symptoms of depression and anxiety were reported in 3.9% and 4.5% of participants, respectively, before COVID-19 and these proportions increased to 29.1% (6.6-fold increase) and 37.8% (7.4-fold increase), respectively at the beginning of pandemic (June-July, 2020) [12]. Higher rates of depressive and anxiety symptoms were observed among women, young people, and those with chronic diseases. Somewhat different results were obtained by researchers from the UK in the large community-based study. The proportion meeting criteria for self-reported anxiety and depression disorders was only slightly higher than pre-pandemic [13].

The frequency and severity of anxiety and depression in patients with the most common bowel diseases during the pandemic are almost not reflected in the studies.

The aim of the study was to evaluate the frequency and degree of anxiety and depression in patients with IBS, IBD, and those with CDI during the Covid-19 pandemic.

Materials and Methods. Study subjects were recruited consecutively at the Republican Clinical Hospital of Moldova between March 2020 and March 2022. The following criteria were used to select patients with IBS: age 18–65 years; symptoms consistent with Rome IV criteria; no clinical signs of malabsorption or inflammatory syndrome; normal calprotectin in stool; no abnormalities on colonoscopy; no abnormalities in laboratory tests (hematology, C-reactive protein, routine biochemical tests); no history of organic diseases associated with abdominal pain and/or stool disorders. Patients with IBD were selected according to the following criteria: age 18–65 years; IBD diagnosed endoscopically plus histologically at least 3 months ago; mild to moderate disease activity. CDI was confirmed by enzymatic analysis of glutamate dehydrogenase and toxins A and B of *Clostridioides difficile* in the feces of patients with nosocomial diarrhea. Patients who had taken psychotropic medication for 4 weeks or less prior to the study were excluded. Patients with severe IBD and CDI were excluded.

Anxiety was assessed using the State-Trait Anxiety Inventory (STAI) developed by Spielberger et al. in 1983. The STAI is the most commonly used measure of non-disorder-specific anxiety and includes 40 self-reported questions: 20 separate questions each for state anxiety (SA) and trait anxiety (TA). The 4-point scale for SA includes answers: not at all, somewhat, moderately so, very much so. The 4-point scale for TA is as follows: almost never, sometimes, often, almost

always. The degree of anxiety was determined using an online calculator (<https://psycho-tests.com/test/spielberger-anxiety-test>). SA and TA were assessed as follows: up to 30 points - no anxiety, 30-45 points - increased anxiety, and more than 45 points - severe anxiety.

Hamilton Depression Rating Scale (HAM-D) was used to assess depression. HAM-D is the oldest tool for determining depression. This scale is assessed by clinicians and consists of 17 items. HAM-D allows the doctor to evaluate not only the presence but also the severity of depression. The sensitivity and specificity of HAM-D are 86,4% and 92,2%, respectively [14].

Continuous data were presented as means ± standard deviations, and categorical data were presented as quantities and proportions for statistical analysis. Group differences were tested using χ^2 test, Fisher's test, and Student's test, as appropriate. The statistics were reported as estimates with 95% confidence intervals for ordinal variables and as p-values for continuous variables, with the level of statistical significance specified as 0,05. All statistical analyses were performed with Microsoft Excel.

The study protocol was approved by the Research Ethics Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy of Moldova and was conducted according to the Helsinki Declaration on Human and Animal Studies.

Results. A total of 30 IBS, 30 IBD, and 30 CDI patients were enrolled in this study. The main characteristics of patients in the study groups are presented in Table 1. Female patients predominated in all study groups without significant differences between groups. The mean age was similar in the IBS and IBD groups and higher in the CDI group.

Table 1

Characteristics of patients with IBS, IBD and CDI

	IBS group n=30	IBD group n=30	CDI group n=30	P value
Female rate (n / %)	20 (66,6)	18 (60)	18 (60)	0,828
Mean age (years)	40,6±10,2	41,4±14,6	51,8±16,3	0,004
Subtypes of IBS				
- C-IBS (n / %)	15 (50)			
- D-IBS (n / %)	8 (26,7)			
- M-IBS (n / %)	7 (23,3)			
Types of IBD				
- UC (n / %)		26 (86,7)		
- CD (n / %)		4 (13,3)		

IBS - irritable bowel syndrome; IBD – inflammatory bowel disease; CDI – *Clostridioides difficile* infection; C-IBS - constipation-predominant IBS; D-IBS - diarrhea-predominant IBS; M-IBS - mixed-type IBS; UC – ulcerative colitis; CD – Crohn's disease.

Depression was significantly more common in the IBS and CDI groups than in the IBD group (86,7%, 86,7%, and 56,7% respectively, $p=0,007$). A mild grade of depression was more common in all study groups (Fig. 1).

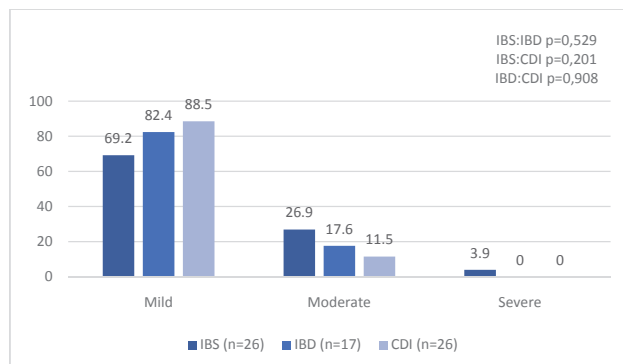


Figure 1. Severity of depression in study groups (among patients with depression, %) (IBS - irritable bowel syndrome; IBD – inflammatory bowel disease; CDI – Clostridioides difficile infection).

Among patients with depression from the IBD and CDI groups, mild depression occurred in the same frequency (82,4% and 88,5%, $p=0,908$), while there were no patients with severe depression. The severity of depression was slightly higher in the IBS group: among patients with depression, 69,2% had mild grades, 26,9% had moderate grades, and 3,9% - had severe grades of depression ($p>0,05$).

The mean depression score reflects the same trend: the most severe situation in the IBS group. The mean score of depression was $13,6\pm6,0$ in IBS group, $12,5\pm5,1$ in CDI group, and significantly lower, $8,3\pm5,6$, in IBD group ($p=0,0008$).

All patients of all study groups had both subtypes of anxiety of varying degrees. Severe state anxiety was found slightly more frequent in the IBS group than in the IBD and CDI groups (60,0%, 46,7%, and 36,7%, respectively; $p=0,192$) (Figura 2). The mean state anxiety score in the IBS group was not higher than in the IBD and CDI groups ($48,6\pm8,8$, $45,9\pm8,9$, $46,7\pm9,3$; respectively; $p=0,483$).

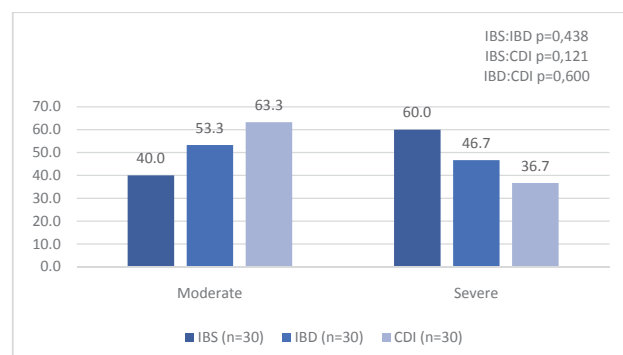


Figure 2. Severity of state anxiety in study groups (%) (IBS - irritable bowel syndrome; IBD – inflammatory bowel disease; CDI – Clostridioides difficile infection).

Trait anxiety was also diagnosed in all patients and was even more frequent and severe than state anxiety. Severe trait anxiety was found more frequent in the IBS group than in the IBD and CDI groups (73,3%; 60,0% and 40,0%; respectively; $p=0,031$) (Figura 3). The mean trait anxiety score was the same in the IBS, IBD, and CDI groups. ($48,8\pm7,3$; $46,4\pm7,6$ and $45,4\pm8,9$; respectively; $p=0,235$).

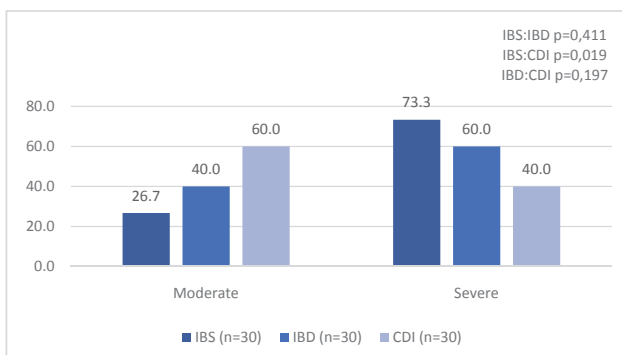


Figure 3. Severity of trait anxiety in study groups (%) (IBS - irritable bowel syndrome; IBD – inflammatory bowel disease; CDI – Clostridioides difficile infection).

Discussion and conclusions. In this study, we investigated the frequency and degree of anxiety and depression in patients with common intestinal diseases during the Covid-19 pandemic. Various studies conducted during the pandemic have revealed that fear of new and poorly understood diseases, social restrictions associated with epidemic measures, and disruptions in work and social activity has led to a significant increase in the frequency of depression and anxiety among the general population [10, 11]. Higher rates of depressive and anxiety symptoms were observed among young persons and those with chronic diseases [12, 15]. A very high frequency of depression (43,3%) and anxiety (45,4%) was found in the cross-sectional online study among young adults (18-30 years) from the U.S. [16]. Another large international study found that patients after COVID-19 had a significantly higher rate of depression compared to controls at the 6-month follow-up [17].

It was logical to assume that the frequency and severity of depression would significantly increase in patients with intestinal diseases during the pandemic period. However, our results even exceeded possible assumptions. The most vulnerable group was found to be patients with IBS, in whom the frequency and severity of depression were highest compared to other groups and significantly exceeded data from previous studies, prior to the pandemic. Thus, according to the results of various studies and their meta-analyses, the frequency of symptoms of depression and anxiety in IBS is on average 20-30% and 35-40%, respectively [2, 3], while

in our group it was 86,7% and 100%, respectively. Moreover, a significant proportion of patients had symptoms of moderate and even severe depression and severe anxiety.

The frequency and severity of depression and anxiety in IBD were lower than in IBS but significantly exceeded data from previous studies. The fact that depression and anxiety are less common in IBD than in IBS is long known [18], and well documented. Nevertheless, different studies indicated that patients with IBD have about a 15-25% prevalence rate of depression and a 20-30% prevalence rate of anxiety [4, 5]. In our study, the frequency of depression was 56,7%, and symptoms of anxiety were found in 100% of patients with IBD.

There are very few studies in the field of psychological disturbance and psychiatric comorbidity in CDI. One of the studies in this field has been devoted to the effect of fecal microbiota transplant on anxiety and depression severity [19]. Using the Hospital Anxiety and Depression Scale (HADS) tool, the authors demonstrated that anxiety and depression levels were 6,28 and 7,37, respectively. These figures were significantly lower than those we obtained in our study. Thus, although it is not entirely correct to compare the data from various studies conducted before COVID-19 using different tools and methods for diagnosing depression and anxiety with the data from our study, it is possible to conclude that there has been a significant increase in the frequency and severity of these disorders in patients with IBD, CDI, and especially IBS.

Our study is subject to several limitations. First, the sample size was small, and tertiary-care patients were included, who may have experienced more distress than other patients. These factors may have influenced the results and led to overestimation of the findings. Another limitation is that the study did not examine subgroups of patients with different types of IBS. However, previous research has shown no significant differences in the levels of depression and anxiety among patients with IBS with diarrhea, constipation, or mixed forms [20, 21], which allows for the analysis of the group as a whole. Similarly, no significant differences were found in this regard for patients with ulcerative colitis and Crohn's disease. Undoubtedly, more extensive research is needed to obtain more accurate data. Nevertheless, the results of our study lead to the overall conclusion that under stressful threatening medico-social conditions, the rate of depression and anxiety becomes extremely high among patients with IBS, IBD, and CDI, and these patients require appropriate diagnosis and treatment.

Declaration about the conflict of interest.

The authors declare no conflict of interest.

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