Irritable bowel syndrome after *Clostridioides difficile* infection

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Abstract

Background. Irritable bowel syndrome (IBS) is a chronic functional disorder characterized by abdominal pain, bloating, and altered bowel habits. Post-infectious IBS (PI-IBS) develops after acute gastroenteritis, including *Clostridioides difficile* infection (CDI). While CDI has been shown to decrease in prevalence during the pandemic era, studies indicate a substantial risk of PI-IBS following CDI, data remaining limited. The aim of the present study was to evaluate the risk of PI-IBS following a CDI and a potential correlation between PI-IBS onset and the severity of CDI.

Methods. This cross-sectional study included 69 patients hospitalized with suspected CDI at a tertiary center for Infectious Diseases, in Romania. Inclusion criteria were: patients >18 years of age with confirmed CDI via polymerase chain reaction. The severity of CDI was assessed based on hospitalization, laboratory parameters, and clinical symptoms. PI-IBS was evaluated six months after CDI using the Rome IV IBS questionnaire and the Bristol Stool Form Scale. Relative risk (RR) was calculated using SPSS software and a p value <0.05 was considered significant.

Results. Among the 38 enrolled patients, 24/38 (63%) were males, while 14/38 (37%) were females. The CDI was confirmed in 14/38 (37%) patients by PCR and the infection was ruled out in 24/38 (63%) patients (control group). PI-IBS developed in 57% of the CDI group compared to 25% in the control group (RR=2.29, 95% CI 0.99–5.23, p=0.04). CDI severity correlated with higher PI-IBS risk, with 90% of hospitalized CDI patients developing PI-IBS (RR=2.72, p=0.0493).

Conclusion. PI-IBS occurred in over half of the patients six months after CDI, with disease severity increasing the PI-IBS risk. These findings highlight the need for proactive management in severe CDI cases to prevent long-term gastrointestinal complications.

Keywords: post-infectious irritable bowel syndrome, *Clostridioides difficile* infection, polymerase chain reaction, epidemiology

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Background and aims

Irritable bowel syndrome (IBS) is characterized by chronic and recurrent symptoms such as constipation, diarrhea, bloating, and abdominal pain, without any detectable biochemical or structural abnormalities using conventional laboratory methods. This condition affects approximately 9-13% of the general population at any given time [1]. Usually, IBS is diagnosed based on recurrent abdominal pain that occurs, on average, at least one day a week over the past three months, accompanied by two or more symptoms, such as abdominal pain alteration in the frequency of bowel movements, and changes in stool consistency. Symptoms must have started at least six months prior, in accordance with the Rome IV diagnostic criteria [2]. Also, post-infectious-IBS (PI-IBS) showed the symptoms described in the diagnostic criteria for IBS alone [3]. These symptoms appear after an episode of acute infectious gastroenteritis, characterized by two or more of the following symptoms: diarrhea, vomiting, fever, and a positive result for the etiological agent in stool samples [4]. From 2011 to 2017, the burden of CDI decreased by 24%. However, during the Coronavirus Disease-19 pandemic, studies mostly indicate a decline in CDI prevalence, likely due to reduced testing and strict infection prevention measures. For this reason, more comprehensive data are needed to fully understand the pandemic's impact on CDI incidence [5-7]. Approximately one-quarter of patients report IBS-like symptoms six months or more after a CDI episode and, for this reason, it is crucial to consider the possibility of PI-IBS when patients with a history of CDI present with persistent gastrointestinal symptoms. Additionally, a longer duration of CDI symptoms is moderately associated with PI-IBS. Given the significant incidence of PI-IBS among CDI patients (among 25%), retreatment for recurrence should only be considered after laboratory confirmation of the diagnosis [8,9,14]. Although there are studies examining the risk of PI-IBS after CDI, available data remain scarce [10]. The aim of the present study was to evaluate the risk of PI-IBS following a CDI and a potential correlation between the onset of PI-IBS and the severity of CDI.

Methods

Study design

In this ambispective (retro-prospective) study, we retrospectively enrolled 69 patients admitted to a tertiary center, the Clinical Hospital of Infectious Diseases, Cluj-Napoca, Romania, a in period between 1st January 2016 and 1st January 2018. Specifically, patients were admitted after an episode of acute gastroenteritis, with suspicion of CDI based on the clinical manifestations (watery diarrhea, sometimes bloody or with mucus, fever, abdominal pain, nausea) in association with the epidemiological history (previous hospital admissions, recent antibiotic therapy, and proton pump inhibitor treatment or chemotherapy). The inclusion criteria were patients >18 years of age with suspicion of CDI in which polymerase chain reaction (PCR) for *Clostridioides difficile* detection was performed. Exclusion criteria were i) patients <18 years of age, ii) patients without CDI suspicion, iii) HIV infected patients, iv) patients who died during the course of this study; v) all previous gastrointestinal tract diseases were excluded based on anamnesis and medical records regarding the patient personal history; vi) other etiological agents were excluded by microbiological analysis from stool samples. Severity of CDI was stratified according to the need for hospitalization or not, and on the basis of different laboratory parameters, such as the level of serum creatinine, C-reactive protein (CRP) and white blood cell count (WBC). Patients were tested for CDI infection at the admission and after 6 months through PCR. Six months after the episode of CDI the PI-IBS condition was evaluated using Rome IV IBS diagnostic questionnaire and Bristol Stool Form Scale [2,3,15,16]. The questionnaires were paper printed and directly filled by the subjects, after being recalled in our center to be evaluated. The average response time was 5 minutes.

Statistical analysis

Data were presented as mean ± standard deviation or as numbers with percentages. To evaluate the association between binary variables the Fisher exact test and odds ratio (OR) with mid-p exact 95% confidence intervals (CI) was calculated with epitools R package. A p value <0.05 was considered significant. The data were analyzed using R Environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria), version 4.3.1.

Results

Patients showed a mean age of 62±16 years. During the course of this study, 31/69 (45%) patients died. Among the 38 patients studied, 28/38 (74%) were living in a urban area and 10/38 (26%) in a rural area. At the same time, 24/38 (63%) enrolled patients were males, while 14/38 (37%) were females. The CDI was confirmed in 14/38 (37%) patients by PCR and the infection was ruled out in 24/38 (63%) patients (control group), as reported in figure 1.

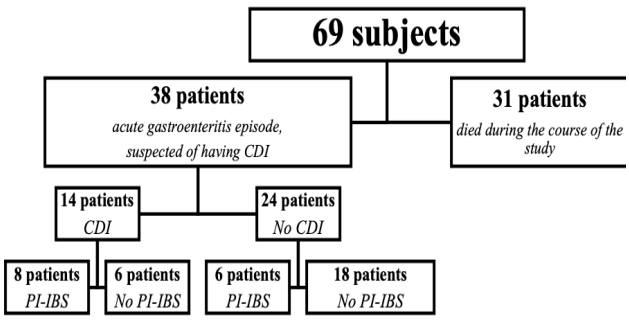

Figure 1. Patients' enrollment workflow.

Table I. Correlation between CDI and IBS.

Patients (N=38)	PI-IBS N=14	No PI-IBS N=24	OR for PI-IBS *OR (95% CI)*	*p* value
CDI (PCR+), n(%)	8 (57%)	6 (43%)	4 (0.94 – 16.99)	0.081
No CDI (PCR-), n(%)	6 (25%)	18 (75%)		

Abbreviations: PI-IBS, post-infectious irritable bowel syndrome; RR: relative risk; CI: confidence interval; CDI, *Clostridioides difficile* infection; PCR, polymerase-chain reaction.

All 38 patients in the studied population completed the above-mentioned questionnaires. Regarding the severity of the disease, 5/38 (13%) patients admitted had fever, 8/38 (21%) vomit, 20/38 (53%) had prior hospitalization, 16/38 (42%) had recently taken antibiotics, 11/38 (29%) showed several comorbidities and were hospitalized for 9±5 days. Within the PI-IBS subgroup, 4 (50%) had cardiovascular comorbidities, 2 (25%) were affected by type 2 diabetes mellitus (T2DM), 1 (12.5%) had recurrent urinary tract infections (UTIs), and 1 (12.5%) suffered from chronic bronchitis. At the same time, within the no PI-IBS group, 3 patients (50%) had cardiovascular comorbidities, 2 (33%) experienced recurrent UTIs, and 1 (16.6%) was diagnosed with T2DM. In contrast, among the 24 patients without CDI, 6 exhibited PI-IBS. Of these, 3 (50%) had cardiovascular comorbidities, 1 (16.6%) had T2DM, and 2 (33%) had Hashimoto's thyroiditis. The remaining 18 non-CDI patients did not have PI-IBS; within this group, 9 (50%) presented with cardiovascular comorbidities, 4 (22%) with T2DM, 3 (50%) with chronic respiratory illnesses, and 2 (11%) had no comorbidities. All patients diagnosed with CDI had a history of prior treatment with cephalosporins, aminopenicillins, and aminoglycosides. In contrast, only four patients without CDI had received prior treatment with cephalosporins. Furthermore, they showed high levels of WBC (>11000/ µl), CRP (>4 mg/dl), and serum creatinine (>1.8 mg/dl). In the CDI group 8/14 (57%) developed PI-IBS after six months, while 6/14 (43%) did not develop PI-IBS. In the control group, 6/24 (25%) patients developed PI-IBS and 18/ 24 (75%) did not develop PI-IBS. After CDI, patients had a higher risk of developing PI-IBS compared to the group where CDI diagnosis was ruled out, with an OR=4(95% Confidence Interval, CI 0.94 – 16.99; *p*=0.081), as showed in table I.

Regarding IBS subtypes, after CDI 62% (5 patients) developed IBS-D, 13% (1 patient) developed IBS-C and 25% (3 patients) developed IBS-M. In the group of patients where CDI was ruled out 17% (1 patient) developed IBS-D, 50% (3 patients) developed IBS-C and 33% (2 patients) developed IBS-M. Regarding the severity of the disease based on hospitalizations, 20/38 (53%) patients were not hospitalized and 18/38 (47%) were hospitalized when recruited for the study. In the group of patients with CDI who required hospitalization 90% (9 patients) developed PI-IBS and 10% (1 patient) did not develop PI-IBS. The odds of PI-IBS were 18 (95% CI 1.15–484.87; *p*=0.036), higher in the group who required hospitalization compared to the group of patients who did not require hospitalization for CDI. In the group of patients without CDI, those hospitalized had an OR=4.33 (0.26–136.58; *p*=0.527) of developing PI-IBS (Table II).

Table II. Correlation between PI-IBS and the severity of CDI.

Patients (N=38)	*CDI (PCR+)* **PI-IBS N=11**	*CDI (PCR+)* **No PI-IBS N=5**	**OR for PI-IBS** *OR (95% CI)*	***p* value**
Hospitalized, *n (%)*	9 (90%)	1 (10%)	18 (1.15–484.87)	0.036
Not hospitalized, *n (%)*	2 (33%)	4 (67%)		
	No CDI (PCR-) **PI-IBS N=3**	*No CDI (PCR-)* **No PI-IBS N=19**	**OR for PI-IBS** *OR (95% CI)*	***p* value**
Hospitalized, *n (%)*	2 (25%)	6 (75%)	4.33 (0.26–136.58)	0.527
Not hospitalized, *n (%)*	1 (7%)	13 (93%)		

Abbreviations: PI-IBS, post-infectious irritable bowel syndrome; RR: relative risk; CI: confidence interval; CDI, *Clostridioides difficile* infection; PCR, polymerase-chain reaction.

Discussion

The aim of the present study was to evaluate the risk of PI-IBS following a CDI and a potential correlation between the onset of PI-IBS and the severity of CDI. We observed that patients who had CDI, evidenced by PCR detection, were at a higher risk of developing PI-IBS. Patients with CDI and previous hospitalizations had a higher risk of developing PI-IBS compared to patients who were not previously hospitalized. The characteristics of the infectious illness such as diarrhea, abdominal cramps, increased stool frequency, bloody or mucous stools, and positive stool culture and weight loss are potent predictors of long-term outcome. At the same time, the risk of PI-IBS appears to correlate with the severity of the acute enteric infection [12,13]. The above-mentioned symptoms are frequently associated with CDI. Wadhwa *et al* [14] showed that 25% of patients with CDI (diagnosed by PCR) without prior IBS develop PI-IBS at least 6 months after CDI which is higher than the mean incidence of PI-IBS in patients due

to infection with other pathogens. Furthermore, patients showed a moderate form of PI-IBS, according to IBS symptoms severity score. In this regard, the results of our study have shown that 57% of CDI patients (8 patients) diagnosed by PCR without a history of IBS have developed PI-IBS and that the CDI severity was a risk factor for PI-IBS. Gutiérrez *et al* [11] carried out a retrospective study on patients who presented CDI The patients were both community-based and hospitalized. The conclusion for both categories of patients was that the incidence of IBS in patients with CDI was higher than in patients who did not have CDI. In our study we observed a higher prevalence of PI-IBS in patients with severe forms if CDI and hospitalized previously compared the patients with mild and moderate forms of CDI who were not hospitalized previously. Thus, CDI is considered one of the major risk factors for PI-IBS patients RR=6.1 (95% CI 2.9-12.9). Our data are in line with this study. Furthermore, a recent systematic review and meta-analysis performed on 15 different studies showed how over 20% of patients develop PI-IBS after CDI, according to our investigation [17]. Also the crucial role of faecal microbiota transplantation (FMT) for CDI was evaluated in a pilot study: In this regard, 2/3 of PI-IBS patients continue to showed diarrheal symptoms up to 6 months after FMT, suggesting the limited application of FMT in PI-IBS [18]. In another study patients with PI-IBS were generally younger and with fewer comorbidities than patients with a diagnosis of CDI alone [19]. This highlights how PI-IBS can affect patients who are young and have risk factors, as contrast to our analysis in which the enrolled subjects have a higher mean age. At the same time, PI-IBS was the most common comorbidity (15%) in 211 CDI patients, followed by inflammatory bowel disease, small intestinal bacterial overgrowth and microscopic colitis [20]. These results, emphasize the importance to perform correct preventive and diagnostic strategies in the different hospital settings [21]. A study found that 3.4% of travelers developed IBS without diarrhea, while 12% of at-risk travelers developed PI-IBS after traveler's diarrhea, with a relative risk of 3.51. The overall PI-IBS incidence following traveler's diarrhea was 12.1%, aligning with meta-analysis data showing an 11.5% prevalence after gastroenteritis [22,23]. Aging is associated with a decline in mucosal immunity, altered gut motility, and a less diverse gut microbiota, all of which may predispose older adults to persistent gastrointestinal symptoms following infection [24]. Moreover, elderly individuals often experience more severe CDI, they are more likely to be hospitalized, and frequently have multiple comorbidities and polypharmacy, which further disrupt gut homeostasis [25]. However, older age was described to be protective against developing symptoms of PI-IBS which is believed to be due to alterations in immunologic response in this age group [26]. For this reason, future studies specifically targeting geriatric populations are warranted to better elucidate the pathophysiological mechanisms behind this condition. Our study presents some limitations: i) the small sample size and its single-center retrospective nature limits the generalizability of the findings, ii) our investigation followed patients for only six months post-CDI, which may be insufficient to fully capture the chronicity or resolution of PI-IBS, as some cases could take longer to develop or resolve, iii) factors such as dietary habits, psychological stress, or co-existing conditions that may influence the development of PI-IBS were not considered, potentially confounding the results. At the same time, the study's strength lies in assessing the specific PI-IBS post-CDI, as other pathogens can also promote this condition. On the one hand, our data demonstrate the urgency of new reliable and robust biomarkers related to CDI and its complications, and, on the other hand, they emphasize the gut microbiota pivotal role in diseases related to the gut-liver axis [5,27].

Conclusions

Our study found that 57% of patients developed PI-IBS six months after a CDI, a significantly higher rate compared to 43% in the control group, where CDI was ruled out by PCR (p=0.04). The severity of CDI was a key risk factor, with 90% of patients who had severe CDI going on to develop PI-IBS.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

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