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Similarities in Clinical and Psychosocial Characteristics of Functional Diarrhea and Irritable Bowel Syndrome With Diarrhea

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Abstract

Background & Aims—There have been few published studies of clinical and psychological characteristics of patients with functional diarrhea (FDr). We studied the clinical and psychological characteristics of patients with FDr presenting to a tertiary care clinic, and compared symptom profiles of FDr with those of IBS-diarrhea (IBS-D).

Methods—Consecutive patients with a diagnosis of FDr (n=48) or IBS-D (n=49), per Rome IV criteria, completed a detailed symptom survey from October 2017 through July 2018. Abdominal pain and diarrhea severity were assessed using patient-reported outcomes measurement information system (PROMIS) questionnaires. Patients with anxiety, depression, or sleep disturbances were identified based on PROMIS T-score of 60 or more. Mean and proportions were compared using the Student *t* test and χ^2 analyses, respectively.

Results—A significantly lower proportion of patients with FDr reported abdominal pain (77.1%) than patients with IBS-D (100%, $P<.001$). The proportion of patients reporting abdominal bloating and level of severity did not differ significantly between groups. Proportions of bowel movements with diarrhea did not differ significantly between groups ($P=.54$), but the mean diarrhea PROMIS T-score was significantly higher among patients with IBS-D ($P=.03$). This difference resulted from the significantly higher levels of fecal urgency-related distress reported by patients with IBS-D ($P=.007$). Proportions of patients with anxiety, depression, or sleep disturbance, and their severities, did not differ significantly between groups.

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Conclusions—In an analysis of about 100 patients with FDr or IBS-D, we found overlap in gastrointestinal and psychosomatic symptoms. These 2 entities appear to be a continuum.

Keywords

chronic diarrhea; Bristol stool form scale; somatization; healthcare utilization

Introduction

Chronic diarrhea affects approximately 7% of the United States (U.S.) adult population and is associated with poor health-related quality of life, increased healthcare utilization and significant loss of work productivity.^{1–5} Despite a thorough investigation, no cause is identified in the majority of cases with chronic diarrhea.^{6,7} The Rome IV consensus statement on functional gastrointestinal disorders classifies chronic diarrhea into two mutually exclusive subgroups: irritable bowel syndrome diarrhea-subtype (IBS-D) and functional diarrhea (FDr).⁸ The diagnosis of IBS-D requires abdominal pain at least one day per week for the last three months and loose or watery stools occurring in >25% of abnormal bowel movements in the last three months.^{1,8} FDr is defined as loose or watery stools occurring in >25% of bowel movements in the last three months without predominant abdominal pain or bothersome bloating.⁸ Patients meeting criteria for IBS-D should be excluded from the diagnosis of FDr.⁸

The worldwide prevalence estimates for FDr in the general population ranges from 1.5% to 17%.^{8–12} However, the literature on clinical characteristics is scarce.⁸ A population based study from China describing the clinical characteristics of individuals with FDr identified diarrhea and urgency as the two most common symptoms.⁹ Data on psychological features in FDr patients are also lacking and Rome IV consensus statement summarizes that “while anxiety often accompanies IBS, few data apply specifically to FDr”.⁸ Better understanding of clinical and psychological characteristics of patients with FDr might give us insight into pathophysiology and treatment options for FDr as the current data on its pathophysiology and treatment are largely extrapolated from IBS-D.⁸

Although the diagnosis of FDr requires excluding those meeting the criteria for IBS-D, Rome IV consensus statement acknowledges that functional bowel disorders (IBS and non-IBS diagnoses) likely exist on a continuum.⁸ No study to date has compared the clinical and psychological characteristics of patients presenting to clinic with FDr to those with IBS-D and it is unclear whether these entities have overlapping or distinct symptom profile. However, similar comparisons between functional constipation (FC) and constipation-predominant irritable bowel syndrome (IBS-C) have reported significant gastrointestinal and psychological symptom-overlap.^{13–15} Thus, the aim of this study was to i) describe demographic, gastrointestinal, and psychological symptom profile of patients with FDr presenting to a tertiary care clinic ii) compare the symptom profile of patients with FDr to those with IBS-D.

Materials and Methods

Consecutive new patients (n=591) presenting to the outpatient Center for Functional Bowel Disorders and GI Motility at Beth Israel Deaconess Medical Center (BIDMC) between October 2017 and July 2018 filled out a detailed symptom survey sent electronically before their initial visit. Data was collected and stored via Research Electronic Data Capture (REDCap), a HIPAA compliant, free, secure, web-based application. Ethics approval was obtained from Institutional review board at the BIDMC.

Patient population

Patients fulfilling the Rome IV criteria for FDr or IBS-D during the survey period were eligible to be included in this study. Patients were evaluated by physicians with expertise in functional gastrointestinal disorders (AL, JN, JI, VR, DF). Medical records were reviewed for at-least six months from the initial visit to ensure they did not have an organic disease to explain their diarrhea.

Gastrointestinal questionnaires

Rome IV questionnaire—Rome IV questions were used to assess the presence of abdominal pain, fecal urgency, and post-prandial diarrhea over the last three months. Rome IV also uses Bristol stool form scale (BSFS) to assess the proportion of bowel movements with loose or watery stools in the last three months.⁸ Specifically, FDr was diagnosed if all the following criteria were met for the last 3 months- loose or watery stools for at-least 30% of stools, diarrhea was reported as the most bothersome symptom, diarrhea onset for at-least 6 month prior to diagnosis, diarrhea occurring when not using drugs or other treatment for constipation and patient did not meet the criteria for IBS. Functional dyspepsia was also diagnosed using Rome IV questionnaire.⁸

Gastrointestinal PROMIS scales—The Patient Reported Outcomes Measurement Information System (PROMIS) is a National Institutes of Health (NTH) set of tools used to provide information on patient outcomes in a variety of fields. PROMIS scales of diarrhea and belly pain were administered to assess the severity of these symptoms in our patients.¹⁶ PROMIS diarrhea and belly pain questionnaire have six and five questions, respectively, both of which assess symptom severity on a 5 point Likert scale over the past 7 days.¹⁶ Higher T-scores on these questionnaires refer to more severe gastrointestinal symptoms.¹⁶

PAGI-SYM—The PAGISYM is a validated scale for assessing overall dyspepsia symptom severity was completed at baseline and 3-month follow-up.¹⁷ It includes 20 items of equal weight assessing symptom severity of the following six subscales over the past 14 days: heartburn/regurgitation, fullness/early satiety, bloating, upper abdominal pain and lower abdominal pain.

Bloating—A single item measuring presence and severity of bloating was assessed using a visual analogue scale of 0 to 100 over the last 10 days.

Non-gastrointestinal questionnaires

PROMIS questionnaires—PROMIS Anxiety 7a, Depression 8a, and Sleep Disturbance 6a questionnaires were administered to every patient¹⁸. The PROMIS Anxiety Scale 7a short form and PROMIS Depression Scale 8a short form consist of seven and eight questions, respectively, and each question has a 5 point Likert scale over the past 7 days.¹⁸ The PROMIS Sleep Disturbance questionnaire consists of six questions with similar response options.¹⁸

Patient Health Questionnaire—The Patient Health Questionnaire 15 (PHQ-15) is a self-administered, validated measure of somatization among patients. It consists of 15 somatic symptoms and each symptom is scored from 0 (not bothered at all) to 2 (bothered a lot) in the past four weeks.¹⁹ PHQ-15 was used as a continuous score and higher scores suggested higher somatization.¹⁹

Healthcare utilization

Patients were asked to report their healthcare utilization in the last 6 months by evaluating-number of emergency department (ED) visits related to gastrointestinal symptoms, number of primary care physician visits where gastrointestinal symptoms were discussed, number of hospitalizations for gastrointestinal symptoms, and number of gastroenterologist visits.

Statistical Analysis

Statistical analysis was performed using Stata 13.0 (StataCorp, College Station, TX). For each PROMIS questionnaire, the total raw score was calculated and transformed to standardized T-score distribution as suggested by the scoring manual.²⁰ This distribution has been established such that the mean value for the healthy US population is 50 and the standard deviation (SD) represents variation of 10. Anxiety, depression and sleep disturbance were defined as a T-score ≥ 60 . Means were reported with 95% confidence interval (CI). Means were compared using Student's t-test. Proportions were compared using chi-square test. P value less than 0.05 was considered statistically significant.

Results

118 patients met the Rome IV criteria for IBS-D or FDr (58 IBS-D and 60 FDr). Of these, 19 patients were found to have other causes to explain their diarrhea [microscopic colitis (n=3), celiac disease (n=11), inflammatory bowel disease (n=1), subtotal colectomy (n=1) and laxative use (n=3)]. Two patients did not have any follow-up and were also excluded. Finally, 97 patients (48 FDr and 49 IBS-D) were included for further analyses.

The majority of the patients with FDr were women (n=36, 75.0%) with a mean age of 49.2 years (± 18.4). Similarly, the majority of patients with IBS-D were also women (n=34, 69.4%) though they were significantly younger (35.1 ± 12.4 years) ($P < 0.001$). There were 6 patients in both groups who had cholecystectomy. One patient had Type 2 Diabetes Mellitus in both groups.

Gastrointestinal and bowel symptoms (FDr and IBS-D)

As shown in Table 1 and Table 2, there was significant overlap in abdominal and bowel symptoms in patients with FDr and IBS-D. All IBS-D patients reported abdominal pain (as required by Rome IV) compared with 77.1% of FDr patients ($P<0.001$). The distribution of frequency of abdominal pain over the past three months in the two groups has been shown in Supplementary Figure 1. Likewise, the mean abdominal pain score was higher in IBS-D compared with FDr ($P<0.001$). However, the proportion of patients reporting abdominal bloating and its severity were comparable between FDr and IBS-D patients (Table 1 and 2). The mean diarrhea PROMTS score was greater in IBS-D than in FDr ($P=0.03$). This was driven by significantly higher fecal urgency related distress reported by IBS-D patients compared to those with FDr ($P=0.007$). (Table 3).

The proportion of patients meeting the Rome IV criteria for functional dyspepsia was more common among patients with IBS-D (47.9%) compared to patients with FDr (33.3%) but it did not reach statistical significance ($P=0.15$). However, the overall severity of upper gastrointestinal symptoms measured using PAGI-SYM was significantly higher in patients with IBS-D as compared to those with FDr ($P=0.006$) (Table 2).

Psychosocial characteristics

Anxiety was present in 37.5% and 34.7% of patients with FDr and IBS-D respectively ($P=0.77$). The prevalence of depression was also comparable between the two groups (18.8% in FDr vs. 22.5% in IBS-D, $P=0.65$). The mean anxiety, depression, sleep disturbance and somatization scores were similar between the two groups (Table 4).

Health-care utilization

Proportion of FDr patients visiting ED or getting hospitalized for gastrointestinal symptoms in the last 6 months was similar to those with IBS-D ($P=0.88$ and 0.23 respectively) (Table 4). There was no significant difference in the number of PCP visits (where gastrointestinal symptoms were discussed) or gastroenterologist visits in the last 6 months between the two groups ($P=0.77$ and 0.29 respectively) (Table 5).

Majority of IBS patients (65.3%, 32 patients) and about half of FDr patients (43.7%, 21 patients) took medications to treat their diarrhea and/or abdominal pain in the six months prior to initial visit ($P=0.03$). More than one-fifth of the patients (20.8% in FDr and 22.5% in IBS-D) used anti-diarrheal medications in the last six months ($P=0.85$) (Table 6). As expected, medications targeting abdominal pain and/or discomfort such as anti-spasmodics and tricyclic antidepressants were more commonly used by patients with IBS-D compared to those with FDr (Table 6).

Discussion

In this study, we described demographic, clinical and psychosocial characteristics of patients with FDr. We found significant overlap in abdominal and bowel symptoms as well as psychosocial characteristics between FDr and IBS-D. Healthcare utilization was also comparable between the two groups.

Abdominal pain was reported by over three-fourth of our patients with FDr. Although commonly present, the reported frequency and severity of abdominal pain was lower among FDr patients. Rome IV requires abdominal pain to be present, on average, one day per week in the last three months for the diagnosis of IBS.⁸ While abdominal pain can be present in patients with FDr, it should not be the predominant symptom. Thus, it is not surprising that abdominal pain is less severe in patients with FDr. Several studies have described a similar difference between IBS-C and FC, where abdominal pain is present in FC but more common and severe in IBS-C.^{13–15,21}

The frequency of loose or watery stools was similar between FDr and IBS-D patients. Prevalence of fecal urgency was also very high in both groups (91.7% in FDr and 100% in IBS-D). Although patients with FDr reported less severe diarrhea PROMIS scores compared to those with IBS-D, this difference was driven by items measuring bothersomeness/impact of fecal urgency. Distress related to fecal urgency in IBS-D may be related to underlying visceral hypersensitivity. A study in constipated patients identified higher prevalence of visceral hypersensitivity in IBS-C patients compared to those with FC.¹⁴ No study to date has compared the presence of visceral hypersensitivity between FDr and IBS-D.

Prevalence and severity of abdominal bloating was also similar between patients with FDr and IBS-D. Rome IV consensus statement recognizes that abdominal bloating should not be a predominant symptom in patients with FDr.⁸ Our study suggests that despite not being a predominant symptom of FDr, bloating is as common and severe in FDr patients as in IBS-D patients. Bloating is common in several functional gastrointestinal disorders and does not have discriminating effect for these conditions (i.e. does not differentiate one functional gastrointestinal disorder from the other except when it is the sole predominant symptom as in functional abdominal bloating and distention).

More than one-third of patients with FDr reported anxiety. About one-fifth of FDr patients also reported depression and sleep disturbance. Others have reported similar prevalence of anxiety and depression in patients with functional gastrointestinal disorders presenting to tertiary care centers.^{22,23} We found that prevalence and severity of anxiety and depression was comparable between IBS-D and FDr patients, while others have reported a higher prevalence of anxiety in patients with IBS-D compared to those with FDr.²⁴ Zhao et al reported that mental health subdomain of quality of life was similar between IBS-D and FDr in a community setting.⁹ However, they did not specifically assess for presence (or severity) of various psychological symptoms.

In comparison to Rome III, Rome IV criteria for the diagnosis of IBS-D requires higher frequency of abdominal pain (3 days per month vs. once per week).^{8,25} Moreover, abdominal discomfort has been removed as the part of diagnostic criteria for IBS.^{8,25} Thus, it is possible that a few patients who would have been classified as IBS-D per Rome III are now classified as FDr per Rome IV criteria. Overall, clinical and psychological symptom profile of patients with FDr and IBS-D seems to be very similar except for higher abdominal pain frequency and severity among IBS-D patients (likely a result of diagnostic criteria). Given the similarities in clinical profile of these two entities and the lack of evidence in treatment for FDr, health care providers could consider using treatments which have shown

efficacy in improving diarrhea in IBS-D patients. Future clinical trials designed specifically for FDr are needed.

More than two-third of patients with FDr in our cohort had seen their primary care physician to discuss their gastrointestinal symptoms and about one-half had also seen a gastroenterologist in the last 6 months. Healthcare utilization by FDr patients was also comparable to those with IBS-D. Several studies have shown that healthcare utilization by IBS-D patients is significantly higher than matched controls suggesting healthcare utilization by patients with FDr is also high.²⁶

Our study has several limitations. Firstly, it is possible that a significant proportion of our patients with FDr or IBS-D have an bile-acid malabsorption (BAM).^{27–29} However, testing for BAM is not routinely available in clinical practice and is common in both FDr as well as IBS-D.^{27–29} It is also possible that a significant proportion of our patients have small intestinal bacterial overgrowth, carbohydrate intolerance/malabsorption which are also common in these patients. Secondly, our patients were seeking consultation at a tertiary care center and thus might not reflect clinical or psychosocial characteristics of individuals with FDr in community. Thirdly, the statistical tests were not adjusted for multiple comparisons. We made 36 comparisons at a nominal alpha level of .05. If the null were true in every case, then one would expect two significant tests by chance (we observed ten significant results). Thus, there is a reasonable chance that some of our significant results could be Type I errors, and our results should be replicated.

Despite these limitations, our study has many strengths. Ours is the first study describing detailed clinical and psychosomatic characteristics of patients diagnosed with FDr using Rome IV criteria and comparing them with IBS-D. These patients were evaluated by gastroenterologists with expertise in functional bowel disorders. Thus, the likelihood of missing organic disease such as celiac disease, inflammatory bowel disease and microscopic colitis is very low.

In summary, FDr is highly prevalent functional bowel disorder which has not been well studied. There is a significant overlap in gastrointestinal and psychosomatic symptoms among FDr and IBS-D patients suggesting these two entities, like IBS-C and FC, appear to be in a continuum. The overlap in clinical and psychological profile of IBS-D and FDr patients in our study is similar to that reported between IBS-C and FC in literature. Studies have shown that more than half of patients with FC also met the definition for IBS. In-fact, a significant proportion of patients who were diagnosed with FC clinically were diagnosed by IBS using Rome IV criteria and *vice-versa*.²⁵ Given this overlap, a few authors have suggested the concept of painful and mild-pain constipation as clinically useful alternative to Rome IV classification of IBS-C vs. FC.³⁰ Given the similarities between IBS-D and FDr, clinicians may consider classifying these patients as painful chronic diarrhea and mild pain or painless chronic diarrhea.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FDr	Functional diarrhea
IBS-D	Diarrhea predominant Irritable bowel syndrome
FC	Functional constipation
IBS-C	Constipation-predominant irritable bowel syndrome
REDCap	Research Electronic Data Capture
PROMIS	Patient Reported Outcomes Measurement Information System
PAGISYM	Patient assessment of gastrointestinal symptom severity
PHQ-15	Patient Health Questionnaire 15

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Background

We studied the clinical and psychological characteristics of patients with FDr presenting to a tertiary care clinic, and compared symptom profiles of FDr with those of IBS-diarrhea (IBS-D).

Findings

In an analysis of about 100 patients with FDr or IBS-D, we found overlap in gastrointestinal and psychosomatic symptoms

Implications for patient care

IBS-D and FDr appear to be a continuum. The higher severity of abdominal pain in patients with IBS-D might be attributed to Rome IV diagnostic criteria. Given the similarities, physicians could consider using treatments that reduce diarrhea in patients with IBS-D for patients with FDr.

Table 1:

Gastrointestinal symptoms in patients with Functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D)

	FDr (n=48)	IBS-D (n=49)	P-value
<i>Presence of bowel and abdominal symptoms</i>	<i>N (%)</i>	<i>N (%)</i>	
Fecal Urgency [†]	44 (91.7)	49 (100)	0.04
Post prandial diarrhea [†]	41 (85.4)	45 (92.8)	0.32
Abdominal pain [†]	37 (77.1)	49 (100)	<0.001
Abdominal bloating [‡]	31 (64.6)	26/47 (55.3)	0.36
Abdominal discomfort [§]	40 (83.3)	48 (98)	0.01
Functional Dyspepsia [†]	16 (33.3)	23/48 (47.9)	0.15

[†]Symptom assessed in the last three months using Rome IV questionnaire

[‡]Symptom assessed in the last ten days using VAS 0 to 100

[§]Symptom assessed in the last seven days using PROMIS

Table 2:

Gastrointestinal symptom severity in patients with Functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D)

	FDr (n=48)	IBS-D (n=49)	P-value
Mean Abdominal pain T-score [†]	53.7 (12.2)	62.1 (8.4)	<0.001
Mean diarrhea T-score [†]	57.5 (10.2)	61.4 (6.8)	0.03
Mean percentage of BMs with BSFS 6 or 7 stool consistency [‡]	67.3 (25.1)	70.4 (24.5)	0.54
Mean abdominal bloating score [§]	32.5 (31.6)	32.5 (34.7)	0.99
Mean PAGI-SYM score	0.87 (0.6)	1.3 (0.9)	0.006

PAGI-SYM refers to patient assessment of gastrointestinal disorder symptom severity

BSFS refers to Bristol stool form scale. Mean values expressed as mean (SD)

[†]Symptom assessed in the last seven days using PROMIS

[‡]Symptom assessed in the last three months using Rome IV questionnaire

[§]Symptom assessed in the last ten days using VAS 0 to 100

Table 3:

Comparison of individual PROMIS-diarrhea questions answered by patients with functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D) using a Likert scale of 1 to 5 for each question.

In the past 7 days [†]	FDr (n=48)	IBS-D (n=49)	P-value
How many days you have loose or watery stools?	3.6 (1.4)	4.0 (1.0)	0.14
How much did having loose or watery stools interfere with your day to day activities?	2.6 (1.5)	3.1 (1.2)	0.13
How much did having loose or watery stools bother you?	2.9 (1.5)	3.3 (1.1)	0.13
How often did you feel like you needed to empty your bowels right away or else you would have an accident?	2.6 (1.3)	2.8 (1.2)	0.44
How much did feeling you needed to empty your bowels right away interfere with your day to day activities?	3.2 (1.2)	2.6 (1.5)	0.06
How much did feeling you needed to empty your bowels right away bother you?	2.9 (1.5)	3.7 (1.1)	0.007

[†] Mean values expressed as mean (SD)

Table 4:

Psychosomatic characteristics of patients with Functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D)

	FDr (n=48)	IBS-D (n=49)	P-value
<i>Psychosomatic characteristics</i> [†]	<i>N (%)</i>	<i>N (%)</i>	
Anxiety	18 (37.5)	17 (34.7)	0.77
Depression	09 (18.8)	11 (22.5)	0.65
Sleep disturbance	10 (20.8)	13 (26.5)	0.51
Mean Anxiety T-score [‡]	54.8 (11.7)	56.8 (10.4)	0.36
Mean Depression T-score [‡]	49.5 (10.5)	50.6 (10.4)	0.60
Mean Sleep-disturbance T-score [‡]	52.2 (9.4)	54.0 (10.4)	0.37
Mean Somatization score [§]	11.1 (5.7)	10.3 (5.9)	0.49

[†]Defined by PROMIS T-score ≥ 60

[‡]Measured using PROMIS questionnaires

[§]Measured using PHQ-15

Table 5:

Health-care utilization for gastrointestinal symptoms in the last six months reported by patients with functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D)

	FDr	IBS-D	P-value
	<i>N (%)</i>	<i>N (%)</i>	
Emergency department visits	9/46 (19.6)	10/48 (20.8)	0.88
Hospitalization	3/48 (6.25) *	5/46 (10.9) **	0.42
Gastroenterology visits	21/47 (44.7)	16/47 (34)	0.29
Primary care visits	30/46 (65.2)	30/44 (68.2)	0.77

* 1 patient hospitalized for C diff infection, 1 for gastrointestinal bleeding, 1 for acute diverticulitis.

** 1 patient hospitalized for C diff infection, 1 for gastrointestinal bleeding, 1 for vomiting after colonoscopy prep, 1 for acute gastroenteritis and 1 for acute pancreatitis.

These events (e.g. C diff, gastroenteritis, pancreatitis) were acute and resolved within a few days.

These events did not explain the patient's gastrointestinal symptoms of pain and/or diarrhea during at-least the past three months. In cases of C diff. and gastroenteritis, symptoms persisted after documentation of negative stool studies.

Table 6:

Most common medications used in the six months prior to evaluation for lower gastrointestinal symptoms by patients with functional diarrhea (FDr) and diarrhea-predominant irritable bowel syndrome (IBS-D)

	FDr (n=48)	IBS-D (n=49)	P-value
	<i>N (%)</i>	<i>N (%)</i>	
Anti-diarrheals	10 (20.8)	11 (22.5)	0.85
Probiotics	7 (14.6)	11 (22.5)	0.32
Peptobismol	7 (14.6)	1 (2.0)	0.03
Rifaximin	3 (6.3)	2 (4.1)	0.60
Anti-spasmodics	2 (4.2)	9 (18.4)	0.03
Bile-acid binders	2 (4.2)	0 (0.0)	0.15
Tricyclic antidepressants	0 (0.0)	4 (8.2)	0.04
Others [†]	0 (0.0)	2 (4.1)	0.16

[†]One patient was using Eluxadoline and other was using Alosetron