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Self-Reported Constipation in Patients with Advanced Cancer: A Preliminary Report

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Abstract

Context—Constipation is often inadequately assessed and underdiagnosed in patients with advanced cancer. Many studies use patient-reported constipation as an outcome.

Objectives—The aim was to compare the accuracy of patient-reported constipation as compared with the modified Rome III (ROME) criteria and to determine the agreement between patient-reported constipation, physician assessment of constipation, and objective assessment of constipation by modified ROME criteria among outpatients with advanced cancer.

Methods—Patients with advanced cancer attending a supportive care clinic were screened. Constipation was assessed using the modified ROME criteria, patient report (yes or no and rated 0-10; 10 = worst possible symptom), and physician assessments (yes or no and rated 0-10).

Results—One hundred patients were enrolled and 50 of 100 (50%) patients met the modified ROME criteria for constipation. Disagreement between ROME criteria and the patient report (yes/no) was found in 33 patients (33%), and between ROME criteria and the physician assessment (yes/no) in 39 (39%). The best combination of sensitivity (0.84) and specificity (0.62) was found with scores $\geq 3/10$ for patient-reported constipation.

Conclusions—We found a high frequency of constipation. The limited agreement with modified ROME criteria suggests that a patient's self-report as yes or no is not useful for clinical practice. Patient self-rating on a 0 to 10 scale (score of three or greater) seems to be the best tool for constipation screening among this population. More research is needed to identify the best way to assess constipation in advanced cancer patients

Keywords

Constipation; assessment; Rome criteria; advanced cancer; palliative care

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Disclosures

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Introduction

Constipation can be defined as infrequent or difficult defecation with a reduced number of bowel movements, which may or may not be abnormally hard, and increased difficulty or discomfort [1]. Constipation is a frequent and distressing symptom in patients with advanced cancer and may affect 40% of patients referred to palliative care and up to 90% of patients treated with opioids [2-5]. Cancer patients experience episodes of chronic constipation from many causes, including medications (e.g., opioids, antiemetics, antidepressants), tumor compression/neural plexus invasion, dehydration, poor oral intake, immobility, metabolic disorders (such as hypercalcemia, hypokalemia, or hypothyroidism), and/or autonomic failure [6, 7]. Untreated constipation may lead to distressing symptoms such as abdominal pain and distention, nausea and/or vomiting, anorexia, urinary retention, mental status changes, and delirium [1, 8]. Severe constipation may lead to obstipation and subsequent life-threatening complications of bowel obstruction or perforation [9].

Constipation is inadequately assessed [10] and underdiagnosed [11]. Assessment of constipation by self-report has been proposed and used by a number of authors [11-15]. Preliminary studies have observed limited correlation between patient-reported outcomes and radiological diagnosis of constipation [3, 16]. The Rome criteria are widely accepted and considered to be the most valid tool for the evaluation of constipation in non-cancer patients [17]. Despite the high frequency of and significant discomfort from constipation, the best practice to screen for constipation in advanced cancer patients has not been established.

The primary purpose of this study was to compare the accuracy of patient-reported constipation with the accuracy of the modified Rome III (ROME) criteria and to determine the agreement between patient-reported constipation (by a 0-10 numeric rating score, a report of yes or no, and five questions about constipation-related symptoms scored 0-10) and objective assessment of constipation using the modified ROME criteria among outpatients with advanced cancer. The secondary aims were to determine the associations among constipation, symptom burden (assessed by the Edmonton Symptom Assessment System [ESAS]) and quality of life and to explore the agreement between patient-reported constipation and palliative care specialists' assessment of constipation.

Methods

The Institutional Review Board at The University of Texas M. D. Anderson Cancer Center approved this study and all patients gave written informed consent.

Patients who attended the Supportive Care Clinic at M. D. Anderson Cancer Center between December 6, 2010 and March 28, 2011 were screened and invited to participate if eligible for this study. Patients aged 18 years or older with advanced cancer were included. Exclusion criteria included patients: with impaired cognition; those who did not speak English; with a diagnosis of inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis) or constant diarrhea; with complete or partial bowel obstruction as determined by the palliative care physician; or with a bowel ostomy.

The study coordinator collected the following patient data: age, sex, ethnicity, religious affiliation, marital status, educational level, type of cancer, date of diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.

Measures

Constipation was assessed using the modified ROME criteria, the patient's report and the physician's assessment.

Modified ROME Criteria—A recent paper from Larkin et al. [11] suggests that, as the evidence base is poor and that there are limited data on many aspects of the assessment, diagnosis and management of constipation in palliative care, recommendations should be based on expert clinical opinion or relevant research findings from other settings. We decided to better explore the problem of constipation in advanced cancer by looking at paradigms that already exist in gastroenterology. Several articles regarding constipation in advanced cancer patients or palliative care patients suggest the use of the ROME criteria for the assessment of constipation in this field [7, 10, 18-22]. The ROME criteria also were used to build a questionnaire to screen for constipation in palliative care [8].

The ROME criteria diagnose functional constipation and provide severity indicators [17]. This questionnaire comprises 17 questions relating to abdominal pain or discomfort (questions 1-8), frequency of bowel movements (question 9), stool consistency (questions 10 and 17), ease of defecation (questions 11-15), and the onset of constipation symptoms (question 16) (Appendix I). Most questions have five possible responses ranging from “never/rarely” to “always.” Question 1 has six possible responses ranging from “never” to “every day.” Answers for questions 2, 3, and 16 are “yes” or “no.” In an effort to better adapt the criteria to the dynamic nature of cancer-related constipation, it was necessary to make some minimal changes to the timeline to make it applicable to cancer patients. We increased the time frame for the irritable bowel syndrome (IBS) questions (question 1) from “the last 3 months” to “one year prior to the diagnosis of cancer.” We similarly decreased the interval for the constipation questions (questions 9-15, 17) from “the last 3 months” to “the last 2 weeks.” Since most cancer patients are already on laxatives, we added the phrase “without the use of laxatives” to the loose-stool question (question 17). All these changes were discussed, reviewed and edited for appropriateness by two medical oncologists and two palliative care physicians.

In palliative care patients, it is recommended to take a full patient history to distinguish current and normal pre-illness bowel disorders [11]. As the ROME criteria propose that patients with IBS be considered separately, we report our results in both ways, for the complete cohort and after removing those patients who screened positive for IBS. In each cohort, we assessed the presence of constipation (ROME criteria, yes/no, 0-10) and the severity of constipation was determined as the sum of the scores for questions 9 to 14 (ROME severity).

Patient-Reported Constipation and Related Symptoms—We collected patient-reported constipation data using a numeric rating score ranging from 0 (no symptom) to 10 (worst possible symptom) (PRC 0-10), and a report of yes or no (PRC yes/no). Patients were asked to rate five constipation-related symptoms using an 11-point numeric rating scale ranging from 0 (no symptom) to 10 (worst possible symptom): crampy abdominal pain, abdominal bloating/fullness, belching, gas feeling, and early satiety. These symptoms have been described in the literature as associated with constipation [1, 16, 18, 20, 23-25].

For the PRC 0-10, PRC yes/no and the five related symptoms, we asked patients to describe their symptoms for the past two weeks to coincide with the ROME assessment for stool frequency, consistency, and discomfort. Specifically, the patient would need a two-week window to assess stool frequency to meet the ROME criterion of “fewer than 3 defecations per week.”

Symptom burden was assessed using the ESAS, a validated self-assessment tool that is one of the most commonly used tools for clinical care in cancer [26]. The ESAS was used to measure the intensity of 10 symptoms experienced in the previous 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, lack of appetite, feeling of well-being, and sleep disturbances) [27-29]. Quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [30, 31].

When the interview was finished, patients were asked to complete a questionnaire about their opioid and laxative consumption. The estimated morphine equivalent daily dose was calculated using an equianalgesic conversion table. We calculated the laxatives' mean equivalent daily dose using the number of laxatives and the dose (e.g., a patient receiving the minimal dose of one laxative would have a score of 1; a patient receiving the minimal dose of two laxatives or twice the minimal dose of one laxative would have a score of 2).

Physicians' Assessment—Based on his or her best clinical judgment, the palliative care specialist taking care of each patient assessed the patient's constipation using an 11-point numeric rating scale ranging from 0 (no symptom) to 10 (worst possible symptom) (MDAC 0-10), and a report of yes or no (MDAC yes/no). For both assessments, physicians were allowed to answer "I do not know."

Statistical Analyses

We report categorical variables as numbers and percentages. We tested the distributions of the continuous variables using the Kolmogorov-Smirnov test and found most to be non-normally distributed. Therefore, we analyzed the data using nonparametric methods, and report continuous variables by their median, with the interquartile range.

To determine the prognostic value of the PRC 0-10 item score for detecting patients with constipation according to the ROME criteria, we summarized sensitivity, specificity, positive and negative predictive value. We used simple unweighted kappa coefficients to test for agreement between PRC Yes/No, PRC 0-10 (using a cutoff of 3), MDAC Yes/No, and MDAC 0-10 (using a cutoff of 3), with the yes/no outcome of constipation using the ROME criteria. We examined the correlations between the continuous score given by the ROME criteria and the score given by PRC 0-10, MDAC 0-10, and opioid and laxative intake by calculating Spearman correlation coefficients. To determine whether patients with constipation, as defined by the ROME criteria, have a higher symptom burden and worse quality of life than patients without constipation, we used a nonparametric Wilcoxon two-sample test to examine the associations between constipation diagnosis according to the ROME criteria and ESAS symptoms (each rated 0-10), five constipation-related symptoms (rated 0-10), the EORTC QLQ-C30, opioid intake, and laxative intake.

For all our statistical analyses, a *P*-value of <0.05 was considered to be statistically significant.

Results

A total of 148 patients were eligible and were approached for the study, and 100 were enrolled (Fig. 1). Patient demographics are summarized in Table 1. Forty-six of the 100 (46%) patients enrolled had been diagnosed with cancer at least two years previously, and 41 of 93 (44%) had a performance status score of 0 or 1.

Fifty of the 100 (50%) patients met the ROME criteria for constipation. (Table 2). Fifteen of the 100 patients met criteria for IBS and when these patients were excluded, 38 (45%) of the

remaining 85 patients met the criteria for constipation. Sixty-three of the 100 (63%) patients had laxatives prescribed, 24 (38%) of whom were receiving two or more laxatives simultaneously. The most commonly prescribed laxatives were senna ($n=54$) and polyethylene glycol ($n=23$).

Evaluation of PRC 0-10 Accuracy

Table 3 shows the sensitivity and specificity of different cutoff scores for PRC 0-10. The cutoff score 3/10 achieved the best combination of sensitivity (0.84) and specificity (0.62), positive predictive value (0.69) and negative predictive value (0.79).

Agreement Between PRC, MDAC and ROME Criteria

Table 2 summarizes the agreement between the yes/no outcome of constipation according to the ROME criteria and the patient- and physician-reported assessments. In both the overall cohort and the cohort excluding patients with IBS, moderate agreement (>0.40) was only observed for PRC 3/10 and not for PRC yes/no, MDAC 3/10, or MDAC yes/no. One exception was that moderate agreement also was observed for PRC yes/no for the IBS excluded cohort.

We found significant correlation between ROME severity and PRC 0-10 ($r=0.61$; $P<0.001$). The correlation between ROME severity and MDAC 0-10 was much lower ($r=0.34$; $P=0.001$). There was a significant correlation between ROME and opioid intake ($r=0.25$; $P=0.015$). Although there was a significant association between PRC and ROME severity, the use of PRC 3/10 resulted in 38% false positive and 16% false negative rates, and PRC yes/no resulted in 33% false positive and 33% false negative rates, respectively (Table 2).

The correlation between ROME severity and patient-reported outcomes was stronger than the correlation between ROME severity and physicians' assessment. Those results suggest that patients' reports of constipation are more reliable than the physicians' opinion.

Factors Associated With Constipation According to the ROME Criteria

There was no significant association between the ESAS score and the presence of constipation according to the ROME criteria. Table 4 shows that three of the five constipation-related symptoms were significantly more severe among constipated patients and there was a non-significant trend toward more severity for the two remaining symptoms (abdominal bloating and early satiety).

The EORTC QLQ-C30 subscale scores did not differ between non-constipated and constipated patients except for cognitive functioning, for which the median scores were 83, interquartile range [IQR] 67-100 for non-constipated patients and 67 (IQR 50-83) for constipated patients ($P=0.05$), and financial difficulties, for which the median scores were 33 (IQR 0-67) for non-constipated patients and 67 (IQR 33-75) for constipated patients ($P=0.04$). As expected, there was a significant difference in scores for the constipation question, for which the median scores were 0 (range 0-33) for non-constipated patients and 33 (range 33-67) for constipated patients ($P<0.001$).

There was a non-significant trend suggesting higher levels of fatigue (EORTC QLQ-C30) for the constipated group; the median score for non-constipated patients was 44 (IQR 22-67) compared with 56 (IQR 33-78) for constipated patients ($P=0.09$).

Table 5 shows that both the opioid and the laxative mean adjusted doses were significantly higher for patients with constipation than for those with no constipation.

Discussion

Among the patients' and physicians' subjective assessments of constipation that we evaluated, the self-reporting tool PRC 0-10 with a cutoff score ≥ 3 had the best combination of sensitivity, specificity, and predictive value. We found a high frequency of constipation (50%). Patients' self-reported constipation as yes/no left almost one-third of patients undiagnosed. The limited sensitivity and specificity of patients' self-reported constipation (yes/no) suggest that it is not useful for clinical practice.

Our findings are similar to those of Noguera et al. [8]. We found that the PRC 0-10 assessment with a cutoff score $\geq 3/10$ had a better sensitivity than that reported by Noguera et al. This might reflect differences in the patient populations or in the treatments. However, both studies confirm the usefulness of a 0-10 patient-reported outcome for the assessment of constipation in advanced cancer patients. Our findings suggest that approximately 16% of constipated patients will not be identified by this assessment. Therefore, individualized assessment should always be conducted, particularly when there are multiple risk factors.

The modified ROME criteria appeared to be effective for detecting constipation because patients diagnosed with constipation according to these criteria had a higher severity of constipation-related symptoms, and received higher doses of laxatives and opioids. The laxative dose can be considered a measure of the diagnosis made by the clinicians, and in this case, there was a strong association between the modified ROME criteria diagnosis of constipation and the doses of laxatives, as well as of opioids.

This study was conducted in a supportive care outpatient center in a comprehensive cancer center specializing in the management of severe symptom distress. The board-certified palliative medicine specialists are highly trained in the evaluation of physical and psychosocial distress. It is likely that the assessment of constipation in this setting is superior to that in other settings because of the body of knowledge on constipation in palliative medicine [32]. Only eight of the 50 constipated patients were not treated with laxatives, suggesting a good rate of identification by the supportive care team. The results regarding the diagnosis and treatment of constipation in other clinical settings such as medical oncology or family practice may be significantly different. More research is needed in this area.

Because of the cross-sectional design of our research, we cannot differentiate patients with constipation that is refractory to laxative treatment from patients who have just started laxative treatment, nor can we differentiate patients without constipation because they were previously treated with laxatives from patients currently taking laxatives and without constipation.

More research is needed to validate the ROME component in cancer patients and to identify the best way to assess constipation in patients with advanced cancer in clinical practice. It is important that efforts to improve detection of constipation are accompanied by efforts to improve its treatment as well.

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Appendix I

Rome Questionnaire – Constipation Module

1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	<ul style="list-style-type: none"> ① Never → ② Less than one day a month ③ One day a month ④ Two to three days a month ⑤ One day a week ⑥ More than one day a week ⑦ Every day 	<i>Skip to question 9</i>
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	<ul style="list-style-type: none"> ① No ② Yes ③ Does not apply because I have had the change in life (menopause) or I am a male 	
3. Have you had this discomfort or pain 6 months or longer?	<ul style="list-style-type: none"> ① No ② Yes 	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
5. When this discomfort or pain started, did you have more frequent bowel movements?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
6. When this discomfort or pain started, did you have less frequent bowel movements?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
8. When this discomfort or pain started, how often did you have harder stools?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often 	

	<ul style="list-style-type: none"> ③ Most of the time ④ Always 	
9. In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
10. In the last 3 months, how often did you have hard or lumpy stools?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
11. In the last 3 months, how often did you strain during bowel movements?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
12. In the last 3 months, how often did you have a feeling of incomplete emptying after bowel movements?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
13. In the last 3 months, how often did you have a sensation that the stool could not be passed, (i.e., blocked), when having a bowel movement?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
14. In the last 3 months, how often did you press on or around your bottom or remove stool in order to complete a bowel movement?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	
15. In the last 3 months, how often did you have difficulty relaxing or letting go to allow the stool to come out during a bowel movement?	<ul style="list-style-type: none"> ① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always 	

16. Did any of the symptoms of constipation listed in questions 9-15 above begin more than 6 months ago?	<input type="radio"/> No <input type="radio"/> Yes	
17. In the last 3 months, how often did you have loose, mushy or watery stools?	<input type="radio"/> Never or rarely <input type="radio"/> Sometimes <input type="radio"/> Often <input type="radio"/> Most of the time <input type="radio"/> Always	

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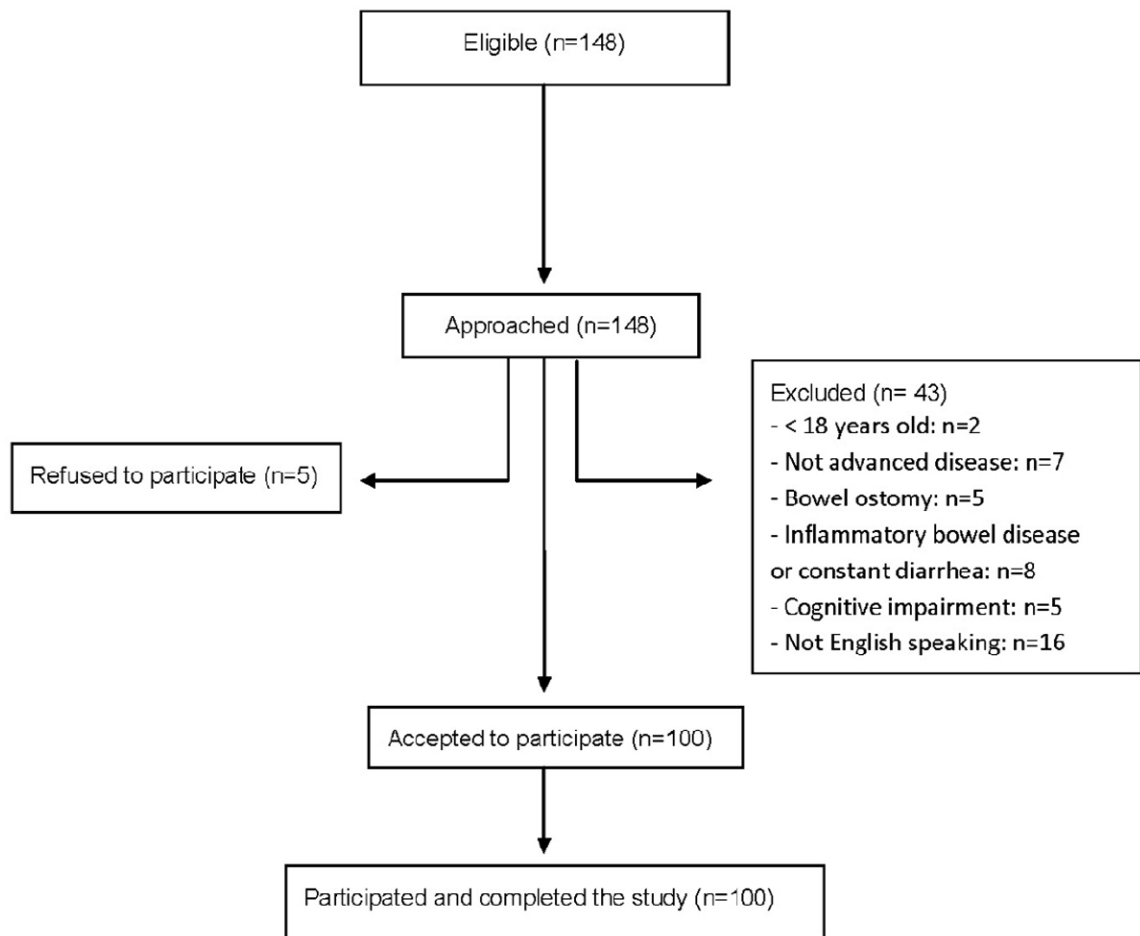


Fig. 1.
Flowchart of the patient selection process.

Table 1

Patient Characteristics (N=100)

Patient Characteristics	n (%)
Female	63 (63)
Married	77 (77)
Highest education level	
High school or below	34 (34)
Any college undergraduate education	54 (54)
Any advanced postgraduate education	11 (11)
Missing	1(1)
Age (years), median (Q1-Q3)	57 (49-65)
Cancer diagnosis	
Breast	15 (15)
Dermatologic	15 (15)
Gastrointestinal	12 (12)
Genitourinary	10 (10)
Gynecologic	9 (9)
Head and neck	4 (4)
Hematologic	6 (6)
Respiratory	18 (18)
Other	11 (11)
ECOG performance status	
0	3 (3)
1	38 (41)
2	35 (38)
3	17 (18)
Missing	7
ESAS items [median (Q1-Q3)]	
Pain	5.0 (2.3-7.0)
Fatigue	5.0 (3.0-7.0)
Nausea	1.0 (0.0-3.8)
Depression	2.0 (0.0-4.0)
Anxiety	2.0 (0.0-5.8)
Drowsiness	3.0 (1.0-6.0)
Shortness of breath	1.0 (0.0-4.0)
Lack of appetite	5.0 (2.0-7.0)
Feeling of well-being	4.0 (3.0-7.0)
Sleep	4.0 (2.0-7.0)
Opioid MEDD median (Q1-Q3)	60 (25-190)

Q1-Q3 = first and third quartiles; ECOG = Eastern Cooperative Oncology Group; ESAS = Edmonton Symptom Assessment System; MEDD = mean equivalent daily dose.

Table 2

Agreement Between Modified Rome III Criteria, Patient-Reported Constipation (PRC 0-10; PRC yes/no) and Physician Assessment of Constipation (MDAC 0-10; MDAC yes/no).

Variables	Complete Cohort (N=100)		Cohen's Unweighted Kappa	Cohort Excluding Patients with IBS (N=85)		Cohen's Unweighted Kappa
	Rome III No Constipation n = 50 (50%)	Rome III Constipation n = 50 (50%)		Rome III No Constipation n = 47 (55%)	Rome III Constipation n = 38 (45%)	
PRC (3) (n=61)	19 (38%)	42 (84%)	0.46	18 (38%)	33 (87%)	0.47
PRC (yes) (n=49)	16 (32%)	33 (66%)	0.34	14 (30%)	28 (74%)	0.43
MDAC (3) ^a (n=49)	19(39%)	30(61%)	0.22	17 (37%)	23(62%)	0.25
MDAC (yes) ^b (n=59)	25 (52%)	34 (71%)	0.19	22 (49%)	25 (69%)	0.20

IBS = irritable bowel syndrome; PRC = patient-reported constipation; MDAC = physician-assessed constipation.

^aTwo patients were assessed as "I do not know."

^bFour patients were assessed as "I do not know."

Table 3
Sensitivity and Specificity of Cutoff Points for Patient-Reported Constipation on a Scale of 0-10

Cutoff Score	Sensitivity	Specificity	PPV	NPV	Number of False Negatives
1	0.92	0.40	0.61	0.83	4
2	0.92	0.50	0.65	0.86	4
3	0.84	0.62	0.69	0.79	8
4	0.74	0.68	0.70	0.72	13
5	0.68	0.72	0.71	0.69	16
6	0.44	0.84	0.73	0.60	28
7	0.38	0.86	0.73	0.58	31

PPV = positive predictive value; NPV = negative predictive value.

Table 4

Constipation-Related Symptom Intensity in Patients With and Without Constipation According to the Modified Rome III Criteria

Variables (scored 0-10)	No Constipation <i>n</i> = 50 Median (Q1-Q3)	Constipation <i>n</i> = 50 Median (Q1-Q3)	<i>p</i> ^a
Abdominal bloating/fullness	1.0 (0-4.0)	2.5 (0.0-5.0)	0.20
Burping/ belching	1.0 (0-3.0)	3.0 (0.0-5.0)	0.044
Crampy abdominal pain	0.0 (0.0-3.0)	3.0 (0.0-6.0)	0.011
Gassy feeling	2.0 (0.0-5.0)	4.5 (2.0-6.0)	0.027
Early satiety	1.5 (0.0-6.0)	4.0 (0.0-7.0)	0.09

Q1-Q3 = first and third quartiles.

^aWilcoxon two-sample test.

Table 5

Comparison of Laxatives Between Patients With and Without Constipation According to the Modified Rome III Criteria

	No Constipation <i>n</i> = 50	Constipation <i>n</i> = 50	<i>p</i> ^a
Opioid MEDD median (range)	45.0 (17.5-8)	91.6 (40.0-330.0)	0.0034
Laxative EDD median (range)	1.5 (0.0-3.0)	3.0 (1.0-6.0)	0.0098

MEDD = mean equivalent daily dose; EDD = equivalent daily dose.

^aWilcoxon two-sample test.