



Published in final edited form as:

*Am J Gastroenterol.* 2008 October ; 103(10): 2536–2543. doi:10.1111/j.1572-0241.2008.01997.x.

## Predictors of Patient-Assessed Illness Severity in Irritable Bowel Syndrome

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### Abstract

**Background**—Conceptual models suggest that “irritable bowel syndrome (IBS) severity” is a multidimensional outcome that is related to, yet distinct from, health-related quality of life (HRQOL). Existing severity questionnaires are largely based on physician rather than patient-based ratings. Since severity is a patient-centered outcome, it is essential that future instruments are based on patients' self-perceptions of severity. We measured patient-derived predictors of severity in a large cohort of IBS patients.

**Methods**—We performed a cross-sectional analysis in 755 IBS patients recruited at a university-based center. Subjects completed a bowel symptom questionnaire, SCL-90, and SF-36. The main outcome was patient-assessed “overall severity of gastrointestinal symptoms,” as measured on a 0–20 scale (20 = most severe). We first developed a conceptual model of IBS, and then performed bivariate analyses to identify biopsychosocial predictors of severity. We then entered significant predictors into a multivariable model to measure the independent association of each predictor with severity.

**Results**—Six factors predicted severity: (a) abdominal pain rating ( $P < 0.001$ ); (b) belief that “something serious is wrong with body” ( $P < 0.001$ ); (c) straining with defecation ( $P = 0.001$ ); (d) myalgias ( $P = 0.02$ ); (e) urgency with defecation ( $P = 0.03$ ); and (f) bloating ( $P = 0.05$ ). Severity correlated highly with HRQOL in bivariate, but not multivariate, analysis.

**Conclusion**—Patient-derived severity in IBS is related to, yet distinct from, generic HRQOL. IBS severity is predicted by abdominal pain, bloating, straining, urgency, myalgias, and disease-related concern. These symptoms fall along both poles of the “brain-gut axis,” indicating that a full assessment of patient severity must include a balanced biopsychosocial history.

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Conflict of Interest

**Potential competing interests:** The opinions and assertions contained herein are the sole views of the authors and are not to be construed as official or as reflecting the views of the Department of Veteran Affairs. There are no competing financial interests.

**Guarantor of the article:** Lin Chang, M.D.

**Specific author contributions:** Drs. Spiegel and Chang formulated the hypotheses and aims of the study, wrote the study protocol, and prepared the manuscript. Dr. Spiegel performed the analyses in concert with Drs. Chang and Strickland. Dr. Strickland performed the literature search, helped formulate the database for analysis, and contributed to the writing of the manuscript. Drs. Chang, Naliboff, and Mayer collected the subject data within their Center's IBS database. Drs. Naliboff and Mayer also provided intellectual input to the manuscript.

## Introduction

Irritable bowel syndrome (IBS) is a disorder of dysregulated brain-gut homeostasis (1,2) primarily characterized by gastrointestinal symptoms such as abdominal pain, bloating, and altered bowel habits (3). Yet many patients also may have concurrent extraintestinal symptoms and disease-specific fears and concerns (4). The heterogeneity of symptom expression suggests that underlying disease mechanisms vary from patient to patient. Experienced clinicians have observed that some IBS patients appear more “brain than gut” in their disease expression, whereas others are more “gut than brain.” The former group may have underlying somatization (5–7), catastrophizing (6,8,9), allostatic overload (4,10), and maladaptive coping (8,11) as central mechanisms of disease expression. The latter group may have abnormal motility, imbalanced intestinal flora (12), or dysregulated intestinal immunity or inflammation as predominant features (13). Moreover, although the “brain *versus* gut” dichotomy may have utility in helping clinicians to stratify patients and develop treatment plans, it is more likely that there are not such clearly defined categories, and instead patients have varying combinations of all these proposed mechanisms.

Despite the heterogeneity of disease mechanisms and expressions, the current clinical paradigm is to adhere all patients with the same IBS label, as recommended by the Rome III committee (3). In the absence of valid and reliable biomarkers to accurately stratify patients within the broader IBS group, clinicians are left interpreting patient-reported symptoms to determine the diagnosis, gauge overall disease severity, and develop rational treatment plans. This presents an extraordinary measurement challenge—namely, to accurately measure the level of illness severity in a varied group of patients while relying on symptomatic epiphenomenon in lieu of biomarkers of underlying disease activity.

Stratifying patients according to severity is of paramount importance in IBS for at least four reasons. First, in everyday clinical practice, IBS patients are typically trichotomized into “mild,” “moderate,” and “severe” groups (14,15). This stratification is critical in helping to determine how to tailor therapy to match their level of severity. Second, because there is no consistent objective marker in IBS, clinical trials rely on patient-reported severity outcomes when testing the efficacy of new treatments (16), which may be only applicable to a subset of patients. Third, the availability of restricted access IBS drugs, such as alosetron and tegaserod, requires that clinicians are capable of selecting the most severe patients when deciding whether to use these drugs. Last, regulatory authorities such as the Food and Drug Administration (FDA) have challenged the validity of existing patient-reported outcomes (*e.g.*, “adequate relief,” “satisfactory relief”), and are increasingly seeking multidimensional outcomes that capture the full disease spectrum (16). In order to develop new patient-reported measures, investigators must first understand what determines severity in IBS from the perspective of patients.

A recent systematic review hypothesized that IBS severity is a multidimensional concept, which includes health-related quality of life (HRQOL), psychosocial factors, health-care utilization behaviors, and burden of illness (14). According to this conceptual model, individual symptoms such as abdominal pain are necessary, but not sufficient, to fully embody severity in IBS. A distinction can be made between “symptom severity,” which is measured by items that ask directly about the intensity or bothersomeness of specific IBS symptoms (*e.g.*, pain, bloating, etc.), and “illness severity,” which includes both symptoms and their impact (*e.g.*, interference of daily activities, extraintestinal symptoms, need for health care, etc.). Illness reflects the patient's experience of their disease including behaviors, attributions, and perceptions. It is not known if a patient's perception of their IBS severity is influenced by specific GI symptoms and/or a range of extraintestinal symptoms, which is not captured by the symptom criteria of IBS.

There are several scales that have been validated for the assessment of gastrointestinal symptom severity in IBS (14,16–18). There are currently only two available multidimensional IBS severity instruments that focus on gastrointestinal symptom severity but also measure health-care utilization or impact on daily functioning: (a) the Functional Bowel Disease Severity Index (FBDSI) (17) and (b) the IBS Severity Scale (IBSSS) (18). Although these instruments are useful to allow physicians to risk-stratify patients by severity, they have several limitations (14), most notably both are physician-derived indices of gastrointestinal symptoms that were not validated from the perspective of patients—the ultimate arbiter of defining severity. In light of these shortcomings, we performed a hypothesis-generating analysis in a large patient cohort to identify clinical predictors of patient self-reported severity in IBS.

## Methods

### Study Patients

We evaluated consecutive patients aged 18 yr or older with Rome I or II positive IBS evaluated at the University of California at Los Angeles Center for Neurovisceral Sciences and Women's Health from 1996 to 2003. The Rome criteria provide a valid and reproducible definition of IBS and are the most stringent criteria for accurately diagnosing IBS (19). The clinical arm of the Center for Neurovisceral Sciences and Women's Health is a university-based specialty clinic that focuses on the evaluation and treatment of patients with disorders of gastrointestinal function. One-third of the patients evaluated at the Center are self-referred through advertising, and two-thirds are referred by primary care providers, community gastroenterologists, and academic gastroenterologists. All of the advertisement and clinic patients who had been referred to the Center were evaluated by one of the gastroenterologists with an expertise in IBS and confirmed the diagnosis by interview. At the time of their initial visit, all subjects evaluated in this study completed a comprehensive Bowel Symptom Questionnaire (20), a psychological symptom checklist (SCL-90R) (21), and the SF-36 Health Survey (22), a validated questionnaire to measure HRQOL. Patients were classified as diarrhea-predominant IBS (IBS-D) if they reported having urgency often and preceded by abdominal cramps, and loose or watery stools without hard stools; constipation-predominant IBS (IBS-C) if they reported having straining often during defecation, and dry, hard stools without loose or watery stools; and IBS with alternating bowel habits (IBS-A) if they reported often having diarrhea alternating with constipation, fluctuations in the number of bowel movements and the consistency of their stool. The study was approved by the University of California at Los Angeles Institutional Review Board and was conducted in accordance with the institutional guidelines regulating human subjects research.

### Primary Outcome Measure

The main outcome was patient-reported overall symptom severity. Patients received the following instruction: “Rate the overall severity of your IBS symptoms during the past week on a scale from 0 (no symptoms) to 20 (the most intense symptoms imaginable).” Patients registered their response by marking 1 number along a 0- to 20-point scale. Numerical rating scales with similar end point anchors have been widely used in the pain literature to measure global pain severity, and have been shown to have excellent face, content, and construct validity in chronic pain conditions (23–25). As IBS is marked by chronic visceral pain and discomfort, it is reasonable to employ the numerical rating scale as a measure of patient-assessed severity. However, because this outcome has not been specifically validated in IBS, we previously conducted a separate set of analyses to measure the cross-sectional construct validity of the scale in a cohort of 170 IBS patients recruited as part of a separate natural history cohort—the IBS Patient-Reported Observed Outcomes and Function (IBS PROOF) cohort. Data from the IBS PROOF cohort revealed that the 0- to 20-point scale correlates with both the FBDSI ( $r = 0.41$ ,  $P < 0.001$ ), IBSSS ( $r = 0.63$ ,  $P \leq 0.0001$ ), and IBS Quality of Life (IBS-QOL) instrument

( $r = 0.41$ ,  $P \leq 0.0001$ ) (26). Moreover, this single-item scale can accurately discriminate between treatment responders *versus* nonresponders in both cross-sectional and longitudinal analyses. Thus, the numerical rating scale has sufficient face, content, and construct validity to serve as a surrogate for patient-reported severity for purposes of a hypothesis-generating cross-sectional correlational study.

### Clinical Predictors of Severity

Because “IBS severity” is a global end point that depends on several factors (14), we developed a conceptual model to specify the relevant variables that might predict how patients report their overall severity. We based our conceptual model upon *a priori* hypotheses guided by empirical data from the literature and existing concepts of IBS severity. Our model posited that IBS severity is related to, yet distinct from, overall HRQOL. We further hypothesized that severity is related to a range of specific intestinal symptoms, including abdominal pain, urgency, bloating, distension, gas, flare duration, and stool form. We also measured the relationship between severity and psychological symptoms, including somatization, energy level, nervousness, sexual symptoms, obsessive compulsiveness, and depression, among others. Finally, we measured the impact of somatic (*e.g.*, non-bowel) pain on severity, as measured by a complaint of muscle aches. In addition to these clinical predictors, we measured a range of demographic characteristics including age, gender, race, income, marital status, and education. Table 1 lists the variables in the conceptual model and their method of categorization.

### Statistical Analysis

We first performed bivariate analyses to measure the relationship of each predictor variable with patient-reported severity. We used the Student's *t*-test for dichotomous variables (mean severity stratified across each dichotomous variable), and measured the Pearson correlation coefficient for linear variables. In order to generate a parsimonious list of variables, and in acknowledgment of the fact that statistical significance does not always correspond with clinical significance, we limited our subsequent regression model to predictors fulfilling explicit criteria in bivariate analysis: (a) for dichotomous variables, the difference in severity scores between patients with and without the variable exceeded an effect size of 0.5 standard deviation, which is considered to be a “medium effect” in clinical studies (27,28); (b) for linear variables, the correlation with severity exceeded  $r = 0.5$ , which is considered to be a “medium” sized correlation (29); and (c) the *P* value for the bivariate relationship was significant at the  $P \leq 0.05$  level. By limiting our analysis to parameters that were both statistically and clinically significant, we attempted to guard against spurious and potentially noninformative results. The predictors selected from bivariate analysis were then entered as independent variables into a multiple linear regression model. Prior to conducting the multivariable analysis, we first performed collinearity testing between independent variables by constructing a correlation coefficient matrix. This was performed to eliminate redundant variables from further analysis. If two variables correlated higher than  $r = 0.8$ , then one of the pair was eliminated. We entered all remaining variables in a forward stepwise regression model to measure the adjusted independent contribution of each clinical predictor on patient-reported severity, as measured by the 20-point scale. We used Stata Statistical Software Release 8.0 (Stata Corporation, College Station, TX) for all the analyses.

## Results

### Patient Characteristics

There were 749 patients with Rome-positive IBS who completed the study questionnaire. The mean age was  $46 \pm 14$  yr and 68% of the cohort were female. The mean severity score on the 20-point scale was  $11.8 \pm 4.4$ . Forty-eight percent of the cohort was recruited through

advertising, and the remainder presented through clinic referrals. There was no difference in self-reported IBS severity between these patient groups ( $P = 0.81$ ). A detailed comparison of the clinical characteristics of these two patient populations has been previously reported (30). Table 1 displays the descriptive statistics for each of the measured variables specified in the conceptual model.

### Clinical Predictors of IBS Severity

Twenty-four variables fulfilled our prespecified criteria for clinical and statistical significance. Because there was no important collinearity between these variables, we entered all of them into a stepwise linear regression model. As shown in Table 2, the final model revealed six additive factors ( $r^2 = 0.33$ ) within three main categories that independently predicted patient-assessed IBS severity: (a) abdominal pain and nonpainful discomfort, *i.e.*, abdominal pain rating ( $P < 0.001$ ) and bloating ( $P = 0.05$ ); (b) altered bowel habits, *i.e.*, straining with defecation ( $P = 0.001$ ) and urgency with defecation ( $P = 0.03$ ); and (c) extraintestinal and psychological symptoms, *i.e.*, belief that “something serious is wrong with body” ( $P < 0.001$ ) and myalgias ( $P = 0.02$ ). Whereas severity correlated highly with HRQOL in bivariate analysis, HRQOL was not an independent predictor of severity in multivariable analysis.

### Discussion

Despite increasing consensus that “severity” is an important outcome measure in IBS for both clinical practice and clinical trials (14), there is uncertainty about how best to measure this construct. Because the most prominent IBS severity questionnaires are largely based on physician rather than patient-based ratings (17,18), we sought to measure patient-derived predictors of severity in a large cohort of IBS patients.

We found that both intestinal and extraintestinal symptoms were associated with patient-reported IBS severity, and their relationship holds after adjusting for patient demographics, disease chronicity, and health-care seeking behavior. This finding comports with previous conceptual models of severity (14), and emphasizes that obtaining a balanced biopsychosocial history (in lieu of a “bowel specific history” but including extraintestinal symptoms) is important to fully understand overall disease burden (31). Unfortunately, evidence suggests that physician and patient perceptions of “severity” often fail to correlate in IBS (32). Moreover, surveys reveal that many providers do a poor job of eliciting their patients' health agendas, addressing their patients' disease-specific fears and concerns, and accurately assessing the impact of IBS symptoms on overall well-being (33–39). Patients, in turn, indicate that this disconnect prompts dissatisfaction with care (33–39). Our finding that IBS severity is associated with intestinal and extraintestinal symptoms adds voice to the growing chorus that patient assessments must include questions that address both poles of the “brain gut axis”—not the gut alone.

We found that IBS severity is strongly related to patient reports of abdominal pain and bloating. Although we did not directly measure visceral perception, a recent study of 109 IBS patients revealed that abdominal pain and bloating are significant predictors of rectal hypersensitivity, thereby suggesting that these symptoms are surrogates for underlying visceral hypersensitivity (40). Our finding that “IBS severity” is strongly associated with abdominal pain and discomfort emphasizes the need to better understand what drives this phenomenon.

In addition to abdominal pain and discomfort, we found that IBS severity is strongly associated with “urgency.” This provides convergent validity to previous definitions of “severe IBS,” such as the definition developed for the alosetron restricted use program. Specifically, the FDA mandated that “severe IBS-D” was defined, in part, by the presence of “urgency,” and that patients must have this symptom in order to be eligible to receive alosetron (41). In addition,

satisfactory control of urgency has been used as a primary outcome in two large clinical trials evaluating the efficacy of alosetron in IBS-D (42,43).

We found that IBS severity is related to “straining.” This is similar to a previous study by Hahn *et al.*, who found that IBS severity is associated with the sensation of “unpassed stool” (44). Of note, a recent study revealed that the symptom of “straining” significantly correlates with rectal sensitivity in IBS-C (45), once again suggesting that IBS severity is partly driven by underlying visceral hypersensitivity. However, our study does not directly measure physiological parameters, and thus we cannot definitively prove this relationship. Future research should explicitly measure the relationship between patient-reported IBS severity, individual symptoms, and visceral hypersensitivity in IBS.

Extraintestinal symptoms, namely somatic pain/discomfort (in the form of “myalgias”), are important predictors of severity in IBS. Previous data indicate that two-thirds of IBS patients report extraintestinal symptoms such as muscle pain (6,46). Furthermore, there is a significant coexistence of IBS with other chronic somatic pain disorders such as fibromyalgia (47,48). The fact that somatic pain is predictive of illness severity in IBS patients is consistent with other findings from the literature, including that the presence of comorbid somatic pain can be associated with increased health-care utilization (5,48,49), and worse IBS illness severity and HRQOL (50).

We found that IBS severity is related to disease-related fears and concerns but not to general mood. Specifically, we found that patients who “feel that there is something seriously wrong with their body” had a significantly higher severity than those who do not share this concern. Anxiety and depression were not significant independent predictors of IBS severity. We previously found that this disease concern also predicts HRQOL in IBS (4). In somatic pain conditions, “pain-specific fear” significantly impacts illness severity and treatment response (51). IBS symptom-specific fears may impact overall severity by prompting avoidance of fear-producing contexts and activities (*e.g.*, restaurants, foods, unfamiliar locations), reinforce “sick role” behaviors (52,53), and/or contribute to the amplification of pain (54).

Guidelines suggest routine HRQOL screening in patients with IBS, and recommend initiating treatment when the symptoms of IBS are found to reduce functional status and diminish overall HRQOL (55). Therefore, HRQOL is now widely considered to be a principal outcome measure in patients with IBS, both in experimental treatment trials and in general clinical practice (55,56). But in this study, generic HRQOL was not independent predictor of severity in IBS. However, generic HRQOL could be distinguished from disease-specific HRQOL, which could be more directly related to illness severity and has been shown to correlate with other measures of treatment effect (57). Our results demonstrate that generic measures of HRQOL in IBS are not adequate surrogates for severity.

This study has limitations. In particular, the university-based referral setting may not be generalizable to all primary care settings. Although one-third of the cohort was self-referred through advertising, two-thirds of the cohort was referred from primary care providers, community gastroenterologists, and academic gastroenterologists. Therefore, many of our patients had already received and failed first-line therapies for IBS. However, we hypothesize that even though severity is likely to be higher in a tertiary referral setting, the determinants of severity in IBS should be similar, regardless of the precise health-care setting. Moreover, we found no difference in overall IBS severity between those recruited through advertising *versus* physician referral. Future studies should further investigate the predictors of severity in individual patient groups, such as those solely from primary care, secondary care, or tertiary care. Another limitation is that the presence of some of the clinical predictors, such as myalgias, individual GI symptoms, and health-related concerns of illness, was assessed using only a

limited number of items. While our analyses support that these factors are significantly associated with IBS severity, the importance and relevance of these predictors were not fully assessed. Further testing with more methodical questioning of these predictors will help to confirm their value and provide a more comprehensive understanding of IBS severity.

Although we selected a broad range of clinical predictors, our list may have omitted important variables. These variables include a disease-specific HRQOL measure and other extraintestinal symptoms such as headache and fatigue. This is evident in the fact that we have only explained one-third of the variance in patient-reported severity ( $R^2 = 33\%$ ). For example, we did not include factors such as current employment status, family dynamics, job satisfaction, or access to health care, among others. Thus, we cannot conclude that these factors are not related to severity or that the results may not be different if they were included. Furthermore, the lack of inclusion of a disease-specific HRQOL measure such as the IBS-QOL did not allow us to definitively determine if the impact of IBS on HRQOL was related to severity. Future studies should address this issue.

In conclusion, our analysis reveals that patient-reported severity in our IBS patient population is highly dependent on gastrointestinal and extraintestinal symptoms and disease-related concern. These symptoms fall along both poles of the “brain-gut” axis, indicating that a full assessment of patient severity must include a balanced biopsychosocial history. These data may assist clinicians in the everyday assessment of patient illness severity in IBS, and may help the broader community of IBS investigators determine what symptoms to target therapeutically, and how best to measure overall severity in future clinical trials.

### Study Highlights

#### What Is Current Knowledge

- Irritable bowel syndrome (IBS) is a heterogeneous condition manifested by multiple gastrointestinal symptoms.
- IBS severity is a multidimensional outcome measure important for clinical practice and clinical trials.
- Existing severity questionnaires are largely based on physician rather than patient ratings.
- There is uncertainty about how best to measure “severity.”

#### What Is New Here

- Patient-derived severity in IBS is related to, yet distinct from, generic health-related quality of life.
- IBS severity is predicted by abdominal pain, bloating, straining, urgency, myalgias, and the belief that “something serious is wrong with body.”
- These symptoms fall along both poles of the “brain-gut” axis, indicating that a full assessment of patient severity must include a balanced biopsychosocial history.

## Acknowledgments

**Financial support:** Dr. Spiegel is supported by a Veteran's Affairs Health Services Research and Development (HSR&D) Career Development Award (RCD 03-179-2), and the CURE Digestive Disease Research Center (NIH 2P30DK 041301-17). Drs. Naliboff, Mayer, and Chang are supported by NIH grant # P50 DK64539, and Drs. Spiegel, Naliboff, Mayer, and Chang are supported by NIH Center Grant 1 R24 AT002681-NCCAM.

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**Table 1**

Descriptive Statistics and for Measured Variables Specified in the Conceptual Model

Variable	Mean (N = 749)	P Value for Bivariate Relationship With Severity
Demographic Variables		
Age (yr)	47 ± 13	0.13
Gender (% female)	72 ± 40	0.5
Ethnicity		
White (%)	78%	0.03
Black (%)	8%	0.88
Asian/Pacific Islander (%)	4%	0.14
Latino (%)	3%	0.09
Other (%)	7%	0.4
Education		
Non-high school graduate (%)	12%	0.2
High school graduate or beyond (%)	88%	0.35
College graduate or beyond (%)	55%	0.96
Professional school graduate (%)	29%	0.02
Marital Status (% married)	24%	0.07
Disease-Specific Patient Variables		
Global disease severity (0–20 VAS, 20 = most severe)	11.8 ± 4.4	–
Global abdominal pain severity (0–20 VAS, 20 = most severe)	11.0 ± 5.3	<0.0001
Global abdominal bloating severity (0–20 VAS, 20 = most severe)	11.3 ± 5.4	<0.0001
IBS Subtype		
IBS-D (%)	43	0.69
IBS-C (%)	22	0.71
IBS-M (%)	34	0.53
IBS flare frequency (% > “several flares per week”)	50%	0.18
IBS flare duration (% flares >24 h)	70%	0.2
Individual IBS Symptoms		
Infrequent bowel movements (% <3 per week)	15%	0.06
Frequent bowel movements (% >3 per day)	33%	0.1
Hard/lumpy stools (% endorsing symptom)	31%	0.056
Loose/watery stools (% endorsing symptom)	70%	0.46
Straining (% endorsing symptom)	37%	0.001
Urgency (% endorsing symptom)	42%	0.03
Incomplete evacuation (% endorsing symptom)	85%	0.014
Mucus (% endorsing symptom)	49%	0.007
Bloating (% endorsing symptom)	82%	<0.0001
Extraintestinal and Psychological Symptoms		
Myalgias (% bothered “quite a bit” or “extremely”)	14%	0.002
Low interest in sex (% bothered “quite a bit” or “extremely”)	14%	0.26
Feeling tense (% bothered “quite a bit” or “extremely”)	16%	0.002

Variable	Mean (N = 749)	<i>P</i> Value for Bivariate Relationship With Severity
Feeling like something serious is wrong (% bothered "quite a bit" or "extremely")	14%	<0.0001
Sleep impairment (0–20 VAS, 20 = most impaired)	11.4 ± 5.5	<0.0001
Health-Related Quality of Life and Psychological Index Scores		
SF-36 Physical Component Score	43.4 ± 10.4	<0.0001
SF-36 Mental Component Score	43.9 ± 10.6	0.001
SCL-90 Somatization Subscale Score	59.6 ± 10.7	<0.0001
SCL-90 Depression Subscale Score	59.7 ± 11.5	<0.0001
SCL-90 Anxiety Subscale Score	55.8 ± 13.2	0.005

The table provides the mean values for each of the included variables, and presents the *P* value for the bivariate relationship between each variable and patient-reported severity (20-point numeric rating scale).

**Table 2**

## Independent Predictors of Patient-Reported Illness Severity in IBS

Symptom	$\beta$ -Coefficient	Standard Error	T-Value	P Value
Abdominal pain rating (0–20 scale)	4.47	0.4	11.2	<0.0001
Belief that “something serious is wrong with body” (dichotomous)	2.05	0.53	3.90	<0.0001
Straining with defecation (dichotomous)	1.06	0.40	2.68	0.01
Myalgias (dichotomous)	1.16	0.48	2.43	0.02
Urgency with defecation (dichotomous)	1.00	0.45	2.21	0.03
Bloating (0–20 scale)	1.02	0.51	2.00	0.05