



Whole Body Pain Distribution and Risk Factors for Widespread Pain Among Patients Presenting with Abdominal Pain: A Retrospective Cohort Study

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ABSTRACT

Introduction: Abdominal pain frequently co-occurs with pain in other body sites. Chronic overlapping pain conditions (COPCs) represent a group of widespread pain diagnoses. Our study characterized how patterns of somatic pain distribution are associated with COPCs and aimed to characterize predictors of widespread pain among patients with chronic abdominal pain.

Methods: This retrospective cohort study included adults presenting to a tertiary pain clinic, reporting abdominal pain at their initial visit, and with a follow-up visit at 12 months. Body maps divided patients into localized, intermediate, and widespread pain distribution patterns. Diagnostic and psychosocial measures were assessed across groups at the initial and

follow-up visits. We analyzed the association of baseline diagnoses and demographics and time-varying changes in psychosocial measures from initial to follow-up visit with changes in pain distribution over time with alternating logistic regression (ALR).

Results: Among 258 patients, most were female (91.5%) and reported widespread pain (61.5%). Those with widespread pain at baseline reported elevated anger and 60.0% of patients remained in the same pain category at follow-up. Multivariable ALR demonstrated higher pain interference (AOR 1.06, 95% CI 1.02–1.10, $P = 0.002$), higher anxiety (AOR 1.05, 95% CI 1.01–1.09, $P = 0.01$), more than one COPC at initial visit (AOR 2.85, 95% CI 1.59–5.11, $P = 0.0005$), and initial visit widespread pain categorization (AOR 4.18, 95% CI 2.20–8.00, $P < 0.0001$) were associated with an increased risk of widespread pain at the follow-up visit.

Conclusion: Most patients with abdominal pain report additional pain locations at multiple other body sites, and non-localized pain persists 12 months after pain treatment. Screening for widespread pain and COPC at the initial visit may identify patients at higher risk for persistent or new-onset widespread pain, and interventions to reduce pain interference and anxiety may promote reversal of widespread pain.

Keywords: Abdominal pain; Body map; Widespread pain; Chronic pain; Chronic overlapping pain conditions

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Key Summary Points

Why carry out this study?

Abdominal pain frequently co-occurs with pain in other locations of the body.

Chronic overlapping pain conditions represent a group of widespread pain diagnoses.

We aimed to characterize the longitudinal changes in somatic pain distribution of patients presenting to a tertiary pain clinic with comorbid abdominal pain over 12 months, and to identify predictors of widespread pain after 12 months of pain treatment including the presence of chronic overlapping pain diagnoses and psychosocial symptoms.

What was learned from the study?

61.5% of patients presenting with abdominal pain at a tertiary pain management center, of which the majority were female, reported widespread pain at their initial visit, and 47.6% of patients reported widespread pain at their 12-month follow-up visit.

Higher pain interference and elevated anxiety symptoms over time were associated with an increased risk of widespread pain at the follow-up visit, while more than one chronic overlapping pain diagnosis, and widespread pain categorization, itself at the initial visit were also significant risk factors for new-onset or persistent widespread pain at the follow-up visit.

Screening for chronic overlapping pain conditions and somatic pain distribution categorization may identify high-risk patients, and interventions to reduce anxiety and pain interference may promote reversal of widespread pain among patients with comorbid abdominal pain.

INTRODUCTION

Chronic abdominal pain is a symptom associated with multiple gastrointestinal disorders and has a significant impact on the healthcare field [1]. Women are particularly affected by chronic abdominal pain, as the prevalence of motility and functional abdominal disorders is high in this population [2, 3]. Abdominal pain remains one of the leading causes of visits to both the emergency room and across ambulatory care settings and is associated with significant healthcare costs [4]. The management of chronic abdominal pain remains a significant challenge for healthcare providers as it involves complex neuroanatomic pathways that incorporate multiple sensory, emotional, and cognitive inputs [5, 6]. Given the complexity of management, extent of increasing disease burden, and cost to the healthcare system, understanding the nature, characteristics, and outcomes for patients with chronic abdominal pain remains an important issue that requires further investigation.

Chronic overlapping pain conditions (COPCs) refer to a group of co-existing pain conditions that include temporomandibular disorders, fibromyalgia, chronic low back pain, headache, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, and irritable bowel syndrome (IBS). Still, the list of associated pain diagnoses is not limited to those mentioned [7]. In addition to pain, patients suffer from associated fatigue, sleep impairment, cognitive impairment, physical dysfunction, and negative affect (e.g., anger, anxiety, depression). The presence of a single COPC significantly increases the likelihood of experiencing additional COPCs compounding negative impacts on overall health.

Patients with certain gastrointestinal disorders such as IBS frequently report pain outside the abdominal region. However, few studies to date have characterized the distribution of body pain among men and women with chronic abdominal pain. It is possible that patients with localized abdominal pain represent a different

patient group than those presenting with widespread pain including the abdominal region [8]. Pain amplification manifesting as widespread pain is a risk factor for heightened dysfunction and lack of treatment response among patients with COPCs. Thus, the distribution of pain over the entire body may have important implications for pain prognosis. The degree of pain distribution from localized to widespread may represent a continuum of increasing pain sensitization [9]. Similar patterns of altered brain structure and function are observed among patients with widespread pain stemming from different, but potentially overlapping, chronic pain diagnoses of fibromyalgia and urologic chronic pelvic pain syndrome [10, 11].

Body maps have been used to characterize somatic pain distribution over the entire body [12]. The body map provides a visual representation of a patient's pain locations [6, 7]. For example, among patients with urologic pelvic pain, an increasing number of body pain sites and more widespread pain are correlated with elevated sensory and affective pain, increased pain severity, sleep disturbance, elevated depression and anxiety, increased psychological stress, and diminished quality of life [13, 14]. Greater somatic pain distribution assessed via the body map is negatively associated with psychosocial health. These findings correlate with heightened levels of depression and anger exhibited by patients with fibromyalgia, for which widespread pain is the cardinal symptom [15], and research suggests anger and sadness as general risk factors for pain amplification among women [16]. Similarly, pain catastrophizing is associated with higher pain intensity among patients with fibromyalgia [17], and patients with fibromyalgia with higher levels of catastrophizing exhibit impaired ability to modulate pain during distraction [18]. Given the treatment-refractory nature of widespread pain [19], identifying significant predictors of chronic widespread pain would help to inform the development of targeted interventions among patients reporting comorbid abdominal pain. Our study aimed to characterize the association between longitudinal changes in negative affect (depression, anxiety, anger) and pain

catastrophizing with the development and persistence of widespread pain among patients presenting with comorbid abdominal pain.

The electronic Collaborative Health Outcomes Information Registry (CHOIR) self-report body map is a validated, digital, general-purpose body map administered to collect self-reported visual body pain locations [20–22]. CHOIR is also used to track patient-reported outcomes to help determine which treatments have been deemed effective and can be used as a representation of different chronic pain conditions of a specific population [21]. This CHOIR body map (CBM) has demonstrated concordance with verbal measures of pain location and has high test–retest reliability [20]. Here we used the CBM to characterize the distribution of pain in a cohort of men and women presenting for care at a tertiary pain management center with a follow-up visit at 12 months. Our study aimed to characterize the distribution of initial pain, changes in pain distribution patterns with the body map, and corresponding changes in pain and mood symptoms among patients reporting concurrent abdominal pain at their initial visit. We hypothesized that elevated psychosocial distress in patients with chronic abdominal pain would be associated with the development of widespread pain.

METHODS

Participants

We prospectively collected data as part of routine clinical care at the Stanford Pain Management Center. All measures and demographics were administered via the Collaborative Health Outcomes Information Registry (CHOIR; <https://choir.stanford.edu>), an open-source learning health system for assessing general- and pain-related health status. CHOIR longitudinally assesses patient-reported outcomes, including mood, pain interference and pain intensity ratings, and body maps. Data for this retrospective cohort study was collected from consecutively enrolled patients presenting for initial medical evaluation at the clinic between November 2013 and September 2018. The study

included patients aged 18 years or older who presented to the pain clinic endorsing abdominal pain (defined on the CHOIR body map as pain in either or both of the two anterior abdominal sites, Fig. 1) and had a follow-up visit 12 months after their initial visit. All aspects of the current study were approved by the Stanford University School of Medicine Institutional Review Board (IRB #28435).

Choir Body Map (CBM)

The CBM is an electronic, visual representation of the body that enables participants to indicate the locations of their pain [20]. A computer mouse or touchscreen device is used to select body areas where patients experience pain with the following instruction: “select the areas where you are experiencing pain” or the option to indicate “I have no pain” [20]. There are 36 anterior segments and 38 posterior segments. There are two body silhouettes of identical segmentation to reflect female and male

anatomy (Fig. 1). Participants selecting “male” or female” gender were provided the respective CBM; those indicating “other” or “decline to answer” were provided the female body map. We collapsed the 74 separate body map areas into nine anatomically defined broader regions as described in a prior study [14]. Figure 1 shows the sites of the CBM included for each of nine body regions: left arm, right arm, left leg, right leg, head, back, trunk, abdomen, and pelvis [14].

Researchers classified patients on the basis of responses to the CBM. The “localized abdominal pain” group consisted of patients that reported pain limited to either of two anterior abdominal sites. Patients who had indicated either anterior abdominal sites and one to three additional pain regions outside the abdomen were categorized to the “intermediate” pain group, and those reporting pain over either anterior abdominal site and four or greater additional pain regions outside the abdomen were categorized to the “widespread” pain group. Categorization was adapted from a

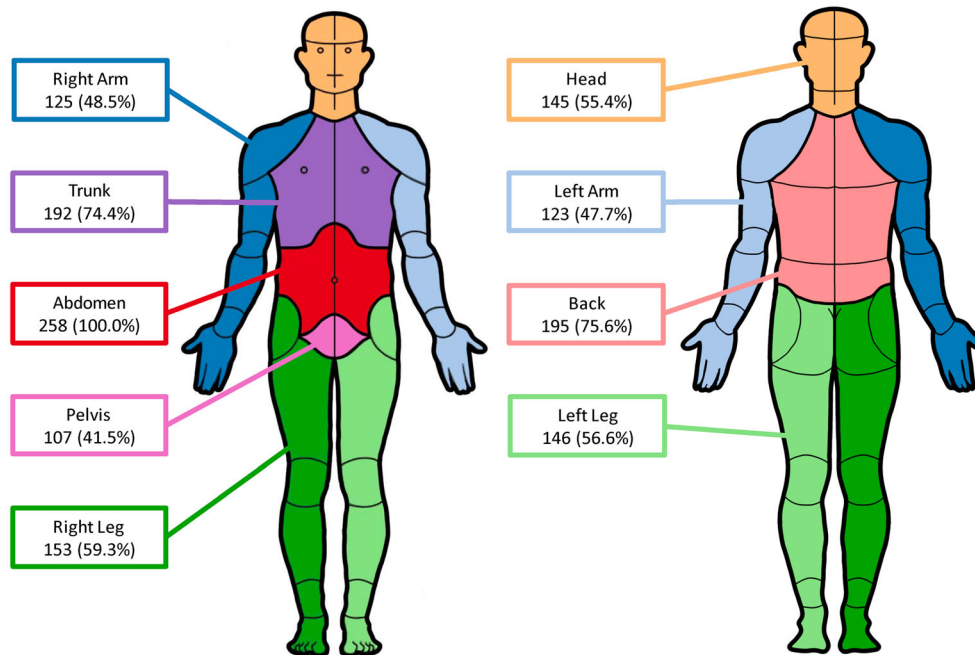


Fig. 1 CHOIR body map pain regions. Left arm = light blue, right arm = dark blue, left leg = light green, right leg = dark green, head = orange, back = coral,

trunk = purple, abdomen = red, pelvis = fuchsia; Regions labeled with number (%) reporting each body map location

Table 1 Demographics, abdominal pain severity, and psychological measures at initial visit

	Men			Women		
	Abdominal pain only	Intermediate	Widespread	Abdominal pain only	Intermediate	Widespread
Patients, <i>n</i> (%)	2 (9.1)	7 (31.8)	13 (59.1)	17 (7.2)	76 (32.2)	143 (60.6)
Age, mean years (SD)	37.7 (20.6)	37.7 (20.7)	37.7 (20.8)	35.8 (13.5)	47.4 (15.1)	46.6 (13.9)
Hispanic ethnicity, <i>n</i> (%)	–	–	3 (13.6)	2 (0.9)	12 (5.1)	17 (7.2)
Race, <i>n</i> (%)						
White	2 (9.1)	5 (22.7)	7 (31.8)	12 (5.1)	50 (21.2)	103 (43.6)
American Indian or Alaskan Native	–	–	–	1 (0.4)	1 (0.4)	3 (1.3)
Asian or Pacific Islander	–	–	2 (9.1)	–	6 (2.5)	6 (2.5)
African American	–	–	–	2 (0.9)	4 (1.7)	7 (3.0)
Other	–	2(9.1)	4 (18.2)	1 (0.4)	13 (5.5)	23 (9.8)
Presence of > 1 chronic overlapping pain condition, <i>n</i> (%)	–	–	2 (9.1)	1 (0.4)	11 (4.7)	41 (17.4)
No. of overlapping conditions (%)						
Irritable bowel syndrome	–	–	1 (4.6)	6 (2.5)	11 (4.7)	28 (11.9)
Fibromyalgia	–	1 (4.6)	2 (9.1)	–	6 (2.5)	30 (12.7)
Chronic fatigue syndrome	–	–	1 (4.6)	–	5 (2.1)	14 (5.9)
Migraines	–	1 (4.6)	4 (18.2)	5 (2.1)	20 (8.5)	47 (19.9)
Endometriosis	b	b	b	–	6 (2.5)	12 (5.1)
Interstitial cystitis	–	–	–	–	1 (0.4)	5 (2.1)
No. of gastrointestinal conditions (%)						
History of bariatric surgery	–	–	1 (7.7)	3 (17.7)	1 (4.0)	13 (9.1)
Celiac disease	–	–	–	–	2 (2.6)	1 (0.7)
Chronic pancreatitis	–	1 (14.3)	–	–	2 (2.6)	1 (0.7)

Table 1 continued

	Men			Women			
	Abdominal pain only	Intermediate	Widespread	Abdominal pain only	Intermediate	Widespread	
Constipation-unspecified cause	–	1 (14.3)	3 (23.1)	5 (29.4)	18 (23.7)	37 (25.9)	0.39
Drug-induced constipation	–	–	–	–	8 (10.5)	12 (8.4)	0.37
Outlet dysfunction constipation	–	–	–	–	4 (5.3%)	3 (2.1)	0.12
Slow-transit constipation	–	–	–	1 (5.9)	6 (7.9)	7 (4.9)	0.19
Crohn's disease	–	–	–	–	3 (4.0)	4 (2.8)	0.36
Ulcerative colitis	–	–	–	–	1 (1.3)	1 (0.7)	0.34
Cyclical vomiting syndrome	–	–	–	1 (5.9)	2 (2.6)	1 (0.7)	0.10
Diabetes mellitus, type 1	1 (50.0)	–	1 (7.7)	1 (5.9)	0 (0.0)	4 (2.8)	0.12
Diabetes mellitus, type 2	–	1 (14.3)	4 (30.8)	–	11 (14.5)	18 (12.6)	0.44
Functional diarrhea	–	–	–	–	0 (0.0)	0 (0.0)	**
Functional dyspepsia	–	–	–	5 (29.4)	12 (15.8)	19 (13.3)	0.23
Functional intestinal disorder	–	–	–	3 (17.7)	4 (5.3)	9 (6.3)	0.50
Gastroparesis	–	1 (14.3)	–	5 (29.4)	9 (11.8)	18 (12.6)	0.44
Gastroesophageal reflux	–	–	–	–	3 (4.0)	6 (4.2)	0.41
Parkinson disease	–	–	–	–	1 (1.3)	0 (0.0)	0.09
Scleroderma	–	–	–	–	1 (1.3)	1 (0.7)	0.34
PROMIS T-score pain interference, mean (SD)	60.0 (5.7)	62.3 (6.2)	70.1 (7.7)	64.6 (8.7)	66.1 (6.3)	67.6 (5.1)	0.02
PROMIS T-score depression, mean (SD)	52.0 (5.7)	48.9 (10.2)	61.2 (10.2)	55.4 (10.9)	55.2 (10.8)	56.6 (8.6)	0.23
PROMIS T-score anxiety, mean (SD)	50.5 (7.8)	46.9 (9.9)	63.5 (10.7)	54.6 (9.7)	56.6 (9.6)	58.6 (8.9)	0.56
PROMIS T-score anger, mean (SD)	43.5 (12.0)	41.9 (11.2)	58.4 (13.3)	48.2 (8.9)	48.9 (9.9)	52.1 (9.2)	0.007
PCS score, mean (SD)	12 (5.7)	17.3 (13.6)	29.1 (10.8)	22.8 (18.8)	22.1 (11.7)	24.2 (11.8)	0.15

Table 1 continued

	Men			Women		
	Abdominal pain only	Intermediate	Widespread P value ^a	Abdominal pain only	Intermediate	Widespread P value ^a
Opioid use, <i>n</i> (%)	2 (9.5)	2 (9.5)	4 (19.1)	4 (1.7)	30 (12.7)	44 (18.6)

n number, *SD* standard deviation, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PCS* Pain Catastrophizing Scale

^aNonparametric Jonckheere–Terpstra test

^bNot applicable

previous body map study among patients with pelvic pain [23]. The CBM was administered at both the baseline and the follow-up visit.

Measures

Demographics

Demographics and medical diagnoses for COPCs (fibromyalgia, chronic fatigue syndrome, migraines, endometriosis, interstitial cystitis) and gastrointestinal conditions were extracted from the electronic medical record for the initial medical visit.

PROMIS Assessments

CHOIR assessments included the National Institute of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) computerized adaptive testing assessments of pain interference, depression, anxiety, and anger. Patients were administered v1.0 versions of PROMIS for anxiety, depression, and anger and v1.1 for pain interference. The PROMIS pain interference item banks assess how pain impacts an individual’s ability to engage in social, physical, cognitive, and emotional tasks [24]. PROMIS anxiety and anger each consist of 29 items and PROMIS depression consists of 28 items. These PROMIS measures are commonly used and valid [25], and further details regarding measure development and validation can be found at <https://www.healthmeasures.net/>. All PROMIS measures are standardized to a mean T-score of 50 and SD of 10.

Pain Catastrophizing

The 13-item Pain Catastrophizing Scale (PCS) is scored with each item rated on a five-point scale from 0 (not at all) to 4 (all the time) with total scores ranging from 0–52. PCS is used to examine three key components: (1) rumination, (2) magnification, and (3) helplessness. Higher scores on the PCS indicate greater catastrophic thinking related to pain. Moderate and clinical levels of catastrophizing are cited as 20 and 30, respectively [26].

The PROMIS measures and PCS were administered at both initial and follow-up

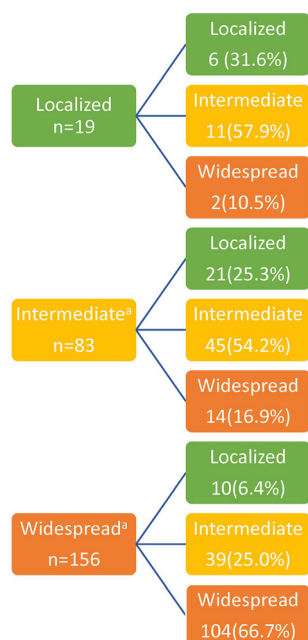


Fig. 2 Pain distribution from initial to follow-up visit. Number (%) for each pain category is reported. ^aThree patients in the intermediate group and three patients in the widespread group at initial visit did not complete the follow-up visit CHOIR Body Map

visits. Self-reported opioid use was assessed as a binary measure at the initial visit.

Statistical Analyses

SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Sample size was determined by the number of eligible patients within the retrospective study period. We had 80% post hoc power to detect an OR of at least 1.05. Less than 3% of patients were missing CBM assessment at the follow-up visit. No imputations or adjustments were performed, and missing data was excluded from the analyses. Mean and SD are reported for continuous variables, and frequencies for categorical variables. To test for a linear gradient effect, ordinal values were assigned to the three pain distribution groups: 3, widespread; 2, intermediate; and 1, localized abdominal pain. Nonparametric Jonckheere–Terpstra trend tests were used to analyze the progression of initial visit measures across the three groups [27]. Chi-

square test for binary variables and Wilcoxon–Mann–Whitney tests for continuous or ordinal variables were used to analyze differences in initial visit measures across the widespread and intermediate pain groups. Initial visit analyses were separated by gender given the limited number of men.

Alternating logistic regression (ALR) was used to analyze the change in CBM pain distribution categorization over time for both men and women. This method adjusts for discrete outcomes measured repeatedly on subjects over time. ALR models associations via odds ratios subject to less restrictive constraints than correlations [28]. ALR allows analysis of multinomial, ordinal outcomes when observations are clustered within subjects [29–31]. It is a specialized case of generalized estimating equations applied via SAS PROC GEE, a generalized linear model often used to incorporate longitudinal data. Multivariate ALR estimated the association of demographics, presence of more than one COPC, widespread pain categorization at the initial visit, and time varying PROMIS pain interference, depression, anger, anxiety, and PCS scores with CBM pain distribution categorization from the initial to follow-up visit. Thus, the ALR analysis predicted the odds of widespread pain categorization at the follow-up visit. The results of the ALR analysis are presented as adjusted odds ratios and 95% confidence intervals. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Initial Visit

A total of 258 patients were included in the analysis. Table 1 describes the demographics and initial visit data. The vast majority were female ($n = 238$, 91.5%) and identified as white ($n = 179$, 69.4%). The age range at baseline for women was 18–81 years of age and for the men 23–68 years. Among men, type 2 diabetes mellitus was the most common co-occurring gastrointestinal condition across groups, followed by constipation. Among women, any category of constipation ($n = 81$, 34%) was the most

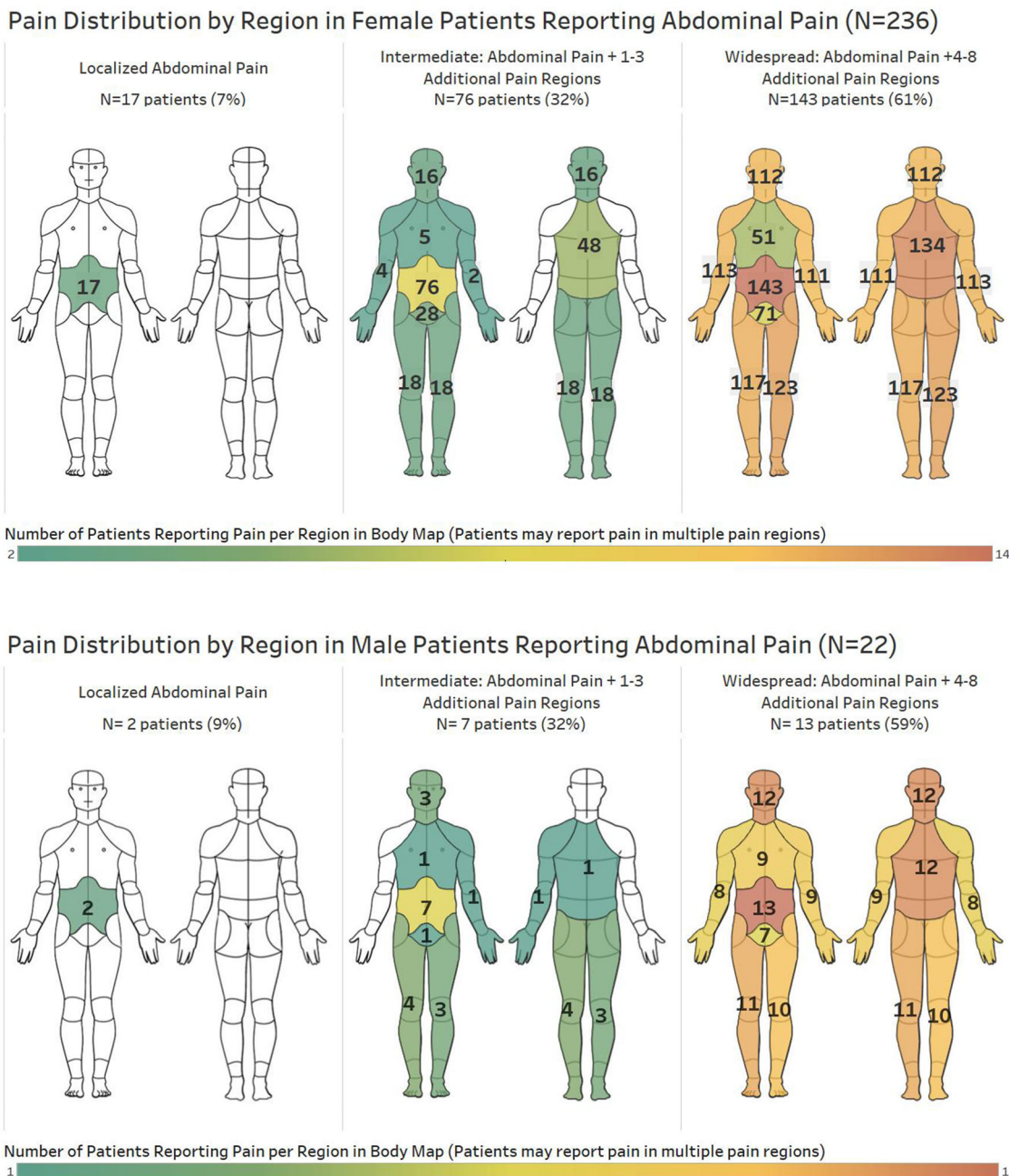


Fig. 3 Heat map of pain distribution patterns. Values indicate number of participants in the three subgroups experiencing pain in a given region

common co-occurring gastrointestinal condition across groups followed by IBS. Figure 2 shows CBM categorization over time. Nineteen (7.4%) patients presented with only localized abdominal pain while 156 (60.5%) patients reported widespread pain at the initial visit.

Table 1 lists the percentage of patients categorized to each CBM pain category stratified by gender at the initial visit. Pain categorization was similar between men and women with a similar proportion reporting widespread and intermediate pain. Among men, PROMIS pain

Table 2 Comparison of intermediate vs widespread abdominal pain groups at initial visit

	Intermediate vs widespread <i>P</i> values ^a	
	Men	Women
No. patients	22	236
Age	0.18	0.87
Psychological measures		
PROMIS T-score pain interference	0.06	0.06
PROMIS T-score depression	0.07	0.48
PROMIS T-score anxiety	0.01	0.17
PROMIS T-score anger	0.012	0.01
PCS score	0.15	0.30
Race	0.81	0.64
Hispanic ethnicity	0.52	0.43
Opioid use	1	0.23
Presence of > 1 chronic overlapping pain condition	0.52	0.02
Chronic overlapping condition:		
Irritable bowel syndrome	1	0.35
Fibromyalgia	1	0.01
Chronic fatigue syndrome	1	0.42
Migraines	0.61	0.312
Endometriosis	^b	0.90
Interstitial cystitis	^b	0.67

n number, *SD* standard deviation, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PCS* Pain Catastrophizing Scale

^aChi-square test for binary variables and Wilcoxon–Mann–Whitney test for continuous or ordinal variables of interest with two-sided significance at $\alpha = 0.05$

^bValues not calculated, no individuals reported for this specific condition

interference and PCS scores showed a progressive increase in scores with increasing pain distribution. Among women, significant

differences in initial visit proportion of patients with more than one COPC or fibromyalgia diagnosis was noted with a greater proportion of affected patients with increasing pain distribution. PROMIS pain interference and anger scores significantly increased from the localized to widespread pain categories. Although 86 (33.3%) reported opioid use at the initial visit, no differences were noted in CBM pain distribution. There were also no differences in the frequency of specific gastrointestinal conditions across groups. Heat maps were constructed to demonstrate the number of participants with pain at specific locations in each of the three pain groups at the initial visit separated by gender (Fig. 3).

We performed additional comparisons between the intermediate and widespread pain subgroups (Table 2). Significantly higher anxiety and anger symptoms were noted in men with widespread pain. Among women, a significantly higher proportion of patients with widespread pain had more than one COPC or a diagnosis of fibromyalgia. In addition, women with widespread pain reported significantly higher anger symptoms.

Follow-Up Visit

Figure 2 demonstrates the CBM pain distribution from the initial to follow-up visit. Overall, 27 patients (10.5%) progressed to a more widespread pain category, 155 patients (60.0%) remained in the same category, and 70 patients (21.7%) moved to a more localized pain category after 12 months. Table 3 reports characteristics for the pain categories from initial to follow-up visit. Overall, PROMIS pain interference, depression, anxiety, and anger scores remained stable over time for each pain category. There appeared to be a trend in general reductions in PCS scores across all pain category groups at 12 months.

In multivariable ALR adjusted for age, gender, race, ethnicity, depressive symptoms, anger symptoms, and PCS score (Table 4), higher PROMIS pain interference scores were associated with widespread pain categorization at the follow-up visit (AOR 1.06, 95% CI 1.02–1.10,

Table 3 Summary of demographics, abdominal pain severity, and psychological measures at initial and follow-up visit

	Initial visit			Follow-up visit ^a		
	Abdominal pain only	Intermediate	Widespread	Abdominal pain only	Intermediate	Widespread
Patients, <i>n</i> (%)	19 (7.4%)	83 (32.2%)	156 (60.5%)	42 (16.7%)	90 (35.7%)	120 (47.6%)
Age, mean years (SD)	36.0 (13.6)	47.9 (15.0)	46.5 (13.6)	45.8 (17.0)	46.9 (14.0)	45.5 (13.4)
Female, <i>n</i> (%)	17 (89.5%)	76 (91.6%)	143 (91.7%)	41 (97.6%)	83 (92.2%)	108 (90.0%)
Hispanic ethnicity, <i>n</i> (%)	2 (11.1%)	12 (14.5%)	20 (13.0%)	8 (19.5%)	10 (11.11%)	16 (13.6%)
Race, <i>n</i> (%)						
White	14 (73.7%)	55 (66.3%)	110 (70.5%)	30 (71.4%)	61 (67.8%)	85 (70.8%)
American Indian or Alaskan Native	1 (5.3%)	1 (1.2%)	3 (1.9%)	0 (0.0%)	3 (3.3%)	2 (1.7%)
Asian or Pacific Islander	0 (0.0%)	6 (7.2%)	8 (5.1%)	1 (2.4%)	5 (5.6%)	6 (5.0%)
African American	2 (10.5%)	4 (4.8%)	7 (4.5%)	4 (9.5%)	6 (6.7%)	3 (2.5%)
Other	1 (5.3%)	15 (8.1%)	27 (17.3%)	5 (11.9%)	14 (15.6%)	23 (19.2%)
Presence of > 1 chronic overlapping pain condition, <i>n</i> (%)	1 (5.3%)	11 (13.3%)	43 (27.6%)	3 (7.14%)	16 (17.8%)	36 (30.0%)
PROMIS T-score pain interference, mean (SD)	64.1 (8.5)	65.8 (6.3)	67.8 (5.4)	64.5 (6.5)	65.4 (7.6)	68.1 (5.3)
PROMIS T-score depression, mean (SD)	55.1 (10.4)	54.7 (10.9)	57.0 (8.8)	53.1 (9.8)	53.7 (9.6)	57.2 (9.4)
PROMIS T-score anxiety, mean (SD)	54.2 (9.5)	55.8 (9.9)	59.0 (9.2)	54.3 (8.5)	55.2 (9.4)	59.8 (9.0)
PROMIS T-score anger, mean (SD)	47.7 (9.0)	48.3 (10.1)	52.6 (9.7)	47.0 (9.9)	48.1 (10.5)	52.3 (10.0)
PCS score, mean (SD)	21.2 (17.8)	21.6 (11.9)	24.8 (11.8)	17.7 (12.9)	16.3 (12.5)	20.2 (13.5)

n number, *SD* standard deviation, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PCS* Pain Catastrophizing Scale

^aSix patients did not complete the body map at the follow-up visit

$P = 0.002$). Similarly, higher PROMIS anxiety scores were associated with widespread pain categorization at the follow-up visit (AOR 1.05, 95% CI 1.01–1.09, $P = 0.01$). The presence of more than one COPC at the initial visit was associated with a significantly increased risk of widespread pain categorization at the follow-up visit (AOR 2.85, 95% CI 1.59–5.11, $P = 0.0005$). As expected, initial visit widespread pain

categorization was associated with a significantly increased risk of persistent widespread pain at the follow-up visit (AOR 4.18, 95% CI 2.20–8.00, $P < 0.0001$).

Table 4 Multivariable alternating logistic regression analysis of the association between pain and mood variables and widespread pain categorization over time

Variable	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	P value
PROMIS T-score pain interference	1.06 (1.03–1.09)	1.06 (1.02–1.10)	0.002
PROMIS T-score anxiety	1.04 (1.02–1.06)	1.05 (1.01–1.09)	0.01
Presence of > 1 chronic overlapping pain condition at initial visit	2.79 (1.62–4.81)	2.85 (1.59–5.11)	0.0005
Widespread pain categorization at initial visit	9.03 (5.31–15.18)	4.18 (2.20–8.00)	< 0.0001

PROMIS Patient-Reported Outcomes Measurement Information System

^aAdjusted for age, gender, race, ethnicity, PROMIS T-score depression, PROMIS T-score anger, and Pain Catastrophizing Scale Score

DISCUSSION

In this study, the majority of patients referred to a tertiary pain clinic reporting pain localized to the abdomen also endorsed pain at multiple other body sites. These trends continued after 12 months of treatment. Also all patients in the study, who were not lost to follow-up, continued to report abdominal pain after 12 months of pain treatment, demonstrating the refractory nature of the abdominal pain. Of note, this cohort is distinct from other diagnoses associated with widespread pain such as fibromyalgia. The presence of chest, abdominal, and jaw pain is not included in the definition of generalized pain for fibromyalgia, and pain localized to the abdomen is not required for the diagnosis of fibromyalgia [32]. Our findings add to existing research by characterizing longitudinal changes in body map pain distribution among patients with refractory chronic abdominal pain. We reported a decreased proportion of patients with widespread pain after 12 months of interdisciplinary pain treatment. Thus, reversal of widespread pain is possible. However, the majority of patients either remained in the same category or reported more widespread pain at the follow-up visit. Through adjusted ALR, we identified the presence of more than one COPC at the initial visit, increased pain interference, and elevated anxiety as significant risk factors for widespread pain despite pain treatment. In addition, widespread pain at the initial visit was

a significant predictor of persistent widespread pain after 12 months. Our study findings emphasize the importance of screening for widespread pain even if treatment is initially sought for localized abdominal pain, as these patients exhibit a refractory course.

At the initial visit, both women and men reporting widespread pain were more likely to report higher pain interference and anger. Among women, higher frequencies of patients with more than one COPC had more widespread pain at the initial visit. Women with interstitial cystitis or bladder pain syndrome reporting widespread pain are more likely to report increased pain severity, additional COPC diagnoses including fibromyalgia, elevated depressive symptoms, and worse quality of life than women with only localized pelvic pain [8, 13]. Similar to our findings, cross-sectional analysis among men and women with urologic chronic pelvic pain demonstrates increased pain interference and a higher proportion of patients with more than one COPC or fibromyalgia diagnosis among patients with widespread body pain symptoms [14]. Our data add to these findings by noting an association of more widespread pain categorization with elevated anger symptoms.

Examination of the degree of pain distribution among patients with chronic abdominal pain has been limited. Among children with IBS or functional abdominal pain, the presence of rectal hypersensitivity was not proportional to

the degree of somatic pain distribution assessed via body map, and other factors are likely to contribute [33]. Rectal distension results in pain at distant sites outside the S3 dermatome among children diagnosed with IBS or functional abdominal pain [34]. For children with chronic abdominal pain, sensations were referred to the T8 to L1 dermatomes [34]. These findings may indicate abnormal projection of sensations through sensitization of enteric neurons, sensitization of spinal cord neurons, and abnormal ascending modulation [34]. We characterized somatic pain distribution among adults reporting concurrent abdominal pain at their initial visit, and similarly note a high percentage of patients report pain symptoms outside of the abdominal region.

Elevations in pain interference as a risk factor for persistent widespread pain may be explained in part by examining the co-occurring gastrointestinal diagnoses of our cohort. Among women, any category of constipation (e.g., slow-transit, outlet dysfunction, drug-induced, unspecified) diagnosis was most frequent. Among adults meeting Rome III IBS criteria reporting abdominal pain in the previous week, individuals with the IBS-constipation subtype report significantly more bothersome abdominal pain, abdominal pain interference of daily activities, and frequent abdominal pain episodes [35]. Thus, the higher percentage of patients suffering from constipation may be driving the association between generalized pain interference and persistent widespread pain in our cohort. Functional magnetic resonance imaging reveals differences in brain activation between patients with constipation or diarrhea-predominant IBS with distinct activation of the mid-cingulate cortex among patients with constipation-predominant IBS not demonstrated in either healthy controls or patients with IBS and diarrhea-predominant symptoms [36]. Thus, a differential response to visceral pain resulting from constipation compared to other causes of abdominal pain may underlie patient-reported pain outcomes in our cohort. Since activation of the mid-cingulate cortex is implicated in integration of negative affect, pain, and cognitive control [37], patients with constipation-predominant gastrointestinal

symptoms may be manifesting exaggerated processing of emotions in response to visceral pain [36].

COPCs describe a group of heterogeneous pain conditions that often coexist in a patient with a high degree of overlap. Patients with COPCs report a higher degree of pain sensitivity, pain amplification, and psychosocial vulnerability [9, 10]. Failure of appropriately diagnosing and treating these heterogeneous conditions often leads to poor overall treatment response [9].

The underlying mechanisms in the development of COPCs have been postulated to occur through peripheral or central sensitization leading to widespread hyperalgesia. IBS is associated with visceral hypersensitivity manifesting as decreased pain thresholds to gut distention. These patients also demonstrate cutaneous hyperalgesia and other extraintestinal symptoms suggesting abnormalities of central nociceptive processing. Compared to patients with IBS alone, those with both IBS and fibromyalgia exhibit somatic hyperalgesia with lower pain thresholds, and higher pain frequency and severity [38]. Research further suggests higher degrees of hyperalgesia present at lumbosacral levels compared to cervical spinal levels among patients with IBS, suggesting viscerosomatic convergence also plays a role in the abnormalities of central nociceptive processing [38]. The presentation of pain both localized and throughout the body differs between patients with isolated IBS and those with comorbid COPCs. Pain amplification and processes mediating pain transmission and modulation play a key role in the maintenance of COPCs [7].

Psychosocial risk factors also play a role in the evolution of COPCs, and many patients suffering from these conditions report heightened depression and anxiety [39]. Psychosocial stress and passive coping skills have also been reported as risk factors. Specifically, among patients free of IBS at baseline, high levels of illness behavior, anxiety, sleep problems, and somatic symptoms were significant independent predictors of IBS onset [40]. Similarly, risk factors for the development of chronic widespread pain among children and adolescents in

a primary care population include mental health diagnoses and gastrointestinal issues [41]. In an 11-year prospective, general population cohort study, anxiety and mixed anxiety and depression symptoms were significant predictors of persistent, chronic widespread pain after a decade [19]. In contrast, isolated depression symptoms did not predict persistent, chronic widespread pain [19]. Similarly, we report significant longitudinal associations between elevated anxiety symptoms and chronic widespread pain among patients with comorbid abdominal pain. Future research in larger cohorts is needed to understand the relative contributions of state and trait anxiety in the persistence of widespread pain, and the efficacy of interventions targeting anxiety to reverse widespread pain symptoms among patients with comorbid abdominal pain.

The degree of pain distribution is likely proportional to the extent of central sensitization. At present, no imaging diagnostics capture this important dimension of chronic pain, and assessment of pain severity alone is less likely to distinguish this group of patients manifesting centralized pain symptoms [14]. Concomitant body pain mapping and screening for COPCs is likely to identify patients at high risk for the development of widespread pain over time.

To our knowledge, this is the first study to evaluate changes in pain distribution patterns over time to better characterize adult patients reporting concurrent abdominal pain at high risk for the progression to widespread pain. We characterized associated mood disturbances in patients with abdominal pain and examined the associations of changes in multiple dimensions of negative affect over time with the development of widespread pain.

Limitations

The study was performed at a single center which may impact its generalizability. Additionally, patients were referred to a tertiary pain center, which may represent a referral bias as these patients may have more refractory and complex pain conditions. Also, by only including patients with a follow-up visit, there may be

a selection bias for patients who did not get better over time. We did not prospectively collect data regarding interim pain treatments patients received, which likely influenced the spread of somatic pain. As a tertiary pain clinic, referring providers are often provided treatment recommendations. Thus, examination of the electronic health record would be incomplete, excluding data for patients prescribed medications or other treatments outside of the pain clinic. Future work to identify beneficial treatments for reversing widespread pain is needed.

The majority of patients in this study were female, and future work is needed to replicate these findings among male patients reporting chronic abdominal pain. However, women are disproportionately affected by chronic pain, and are more likely to suffer from pain conditions with greater severity and extended courses. This trend persists among patients with IBS with an over-representation of female patients in a 3–5:1 setting receiving tertiary care in Western countries [42]. Female patients diagnosed with IBS are more likely to suffer increased abdominal pain and discomfort compared to their male counterparts [42]. Among women, earlier age at menarche is associated with an increased risk of both chronic abdominal pain and chronic widespread pain, potentially highlighting the biologic basis for sex differences in chronic pain symptoms [43]. Thus, women with refractory chronic abdominal pain are more likely to present for treatment at a tertiary pain clinic, and personalized interventions should be targeted to this high-risk population. In addition, women are more likely to develop chronic overlapping pain conditions [44]. Despite the preponderance of female patients in our study, the association between persistent widespread pain and elevated anxiety is consistent with prior research demonstrating the association between elevated anxiety and an increasing number of comorbid chronic overlapping pain conditions including IBS in a cross-sectional cohort of women and men [44].

CONCLUSIONS

Among patients presenting for tertiary pain care reporting abdominal pain, greater pain interference, elevated anxiety, and chronic overlapping pain diagnoses predispose patients to widespread pain despite interdisciplinary pain care. In addition, widespread pain at the initial visit was a significant predictor of widespread pain after 12 months in our study cohort. Our study supports CBM pain categorization among patients with abdominal pain symptoms. Clinically categorizing patients with the CBM and concurrent screening for COPCs is likely to facilitate identification of higher-risk patients, inform disease prognosis, and aid in development of targeted pain interventions.

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Compliance with Ethics Guidelines. Ethical approval was provided by the Institutional Review Board (IRB) of Stanford University, Stanford, California (IRB #28435). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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