Daily Pain Experiences in Chronic Pancreatitis

Identifying Pain Phenotypes

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Objectives: Pain, the hallmark symptom of chronic pancreatitis (CP), remains difficult to assess. To capture the variability of pain that patients can experience day to day, this study used pain diaries to describe daily pain experiences and identify pain phenotypes.

Methods: This study is a secondary data analysis from a pilot trial examining cognitive behavioral therapy for pain treatment in CP. Before treatment, patients completed an online daily pain diary using the Brief Pain Inventory for 7 days. Using indicators of pain magnitude, pain variability, pain synchrony along with least, worst, and average pain intensity levels, we identified pain patterns using K-means clustering.

Results: Of 30 patients in the pilot trial, a total of 27 patients (mean age of 49.8 years, 80% women) had complete data to include in this report. Four clusters were identified: cluster 1, lowest pain magnitude (n = 3); cluster 2, moderate pain magnitude and high pain variability (n = 4); cluster 3, moderate pain magnitude and low pain variability (n = 9); and cluster 4, highest pain magnitude and lowest pain variability (n = 11).

Conclusions: Daily pain diaries offer a novel way of evaluating the dynamic pain experiences in CP. Although 4 distinct pain patterns were identified, further studies are needed to validate these findings.

Key Words: pain, chronic pancreatitis, pain assessment, quality of life

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Pain, the most common symptom in chronic pancreatitis (CP), remains difficult to both assess and manage. Limited in our understanding of the mechanisms of pain in CP, current theories suggest that pain can arise from chronic inflammation, structural complications, and central sensitization.[1] Aside from understanding the pathophysiology of pain, challenges abound in the characterization of pain in CP. Although individuals with CP will typically report epigastric pain that can radiate to the back, the nature of their pain can range from dull to sharp, from aching to nagging.[2] Furthermore, the intensity of pain can vary within and between days, and individuals may experience variability in the frequency of pain from sporadic pain to constant pain.[3,4]

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Prior studies have focused on identifying pain patterns; for example, in an early study in individuals with CP, Ammann and Muellhaupt[5] categorized "A-type pain" as short-lived episodes lasting <10 days that are separated by long pain-free intervals and "B-type pain" where pain is persistent for prolonged periods. The North American Pancreatitis Study-2 (NAPS2) slightly expanded upon this binary classification, incorporating severity with time course to categorize pain as being either mild-to-moderate or severe and intermittent or constant in nature.[3]

Pain patterns are considered critically important in defining the patient experience because they are associated with patient-reported outcomes such as quality of life in the CP population. The NAPS2 study found a significant association between severe pain and lower mental and physical quality of life.[6] In a large cross-sectional study, the Dutch Pancreatitis Study Group found that patients with continuous pain had greater severity of pain, used more opioids, and had a lower quality of life.[4] Relatedly, a 2-center study from New Zealand revealed an association between constant pain and greater pain spread and severity, central sensitization, pain catastrophizing, and lower quality of life.[7]

Nevertheless, the cross-sectional and retrospective nature of prior studies limits understanding of pain patterns including the evolution of pain over time and daily fluctuations of pain. Real-time assessment of daily pain reduces recall bias, and this greater precision in characterizing pain may allow us to understand pain phenotypes with more confidence. For example, pain diaries have led to the identification of pain phenotypes in chronic pain conditions such as fibromyalgia, osteoarthritis, and postsurgical states.[8–11] Therefore, the aim of this study was to use microlevel daily pain experiences to identify different pain phenotypes in a CP population, and to examine the association between phenotypes and patient-reported outcomes.

MATERIALS AND METHODS

Design and Setting

This is a secondary analysis using baseline data from a pilot trial testing the feasibility and preliminary effect of an internet cognitive behavioral therapy intervention for painful CP. Study design and outcomes for the trial have been published previously.[12] Before randomization, participants completed a 7-day online daily pain diary and provided other demographic, clinical, and psychosocial information. Prerandomization (baseline) data were used for the current analysis.

Participants

A total of 30 participants were recruited into the pilot trial between March 2018 and December 2019 from outpatient pancreas clinics and from the community as one goal of the pilot trial was to test feasibility of recruitment procedures. Five clinical sites referred patients (Indiana University, Mayo Clinic, University of Minnesota, University of Pittsburgh, and The Ohio State University). These sites are all part of the Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Consortium, a National Institutes of Health–funded consortium involving 9 sites in the United States with the primary

objective of identifying and characterizing a large cohort of patients with CP to better understand its natural history and develop means of diagnosis and treatment.[13] Potential subjects were also recruited from the community via social media channels of the National Pancreas Foundation.

Inclusion criteria were (1) age greater than 18 years, (2) diagnosis of either suspected (ie, early stage) or definite CP as described hereafter, (3) having personal Internet access, and (4) having experienced moderate pain intensity (rated as 4 or higher on a 0–10 scale) in the last month.[13] Exclusion criteria were (1) undergoing treatment for cancer, (2) unable to read English well enough to complete questionnaires, (3) having current suicidal ideation, or (4) currently receiving treatment from a psychologist. Specifically, definite CP was defined as having obvious morphological features of CP (ie, Cambridge 3–4 stage or the presence of pancreatic calcifications on computerized tomography scan and/or magnetic resonance cholangiopancreatography, or histological evidence of CP). Suspected CP was defined as abdominal pain of 3-month duration or more, 1 episode of acute pancreatitis in the preceding 18 months, or recurrent acute pancreatitis who had Cambridge stage 1 or 2 on computerized tomography imaging, and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography.

Measures

Pain Diaries

Participants completed an online daily diary administered via REDCap assessing pain intensity and pain interference using the 24-hour version of the Brief Pain Inventory—Short Form (BPI) over 7 consecutive days.[14,15] The diary link was sent once in the evening and expired within 24 hours. The 4 pain intensity items (worst, least, average, and current pain) were rated at the end of the day on an 11-point numerical rating scale (0 for no pain, 10 for worst possible pain). Diary data for the worst, least, and average pain were used for the current analysis. The pain interference subscale includes 7 items evaluating the impact of pain on sleep, mood, walking ability, general activity, work, relationships, and enjoyment of life over the past 24 hours rated on an 11-point scale from 0, "does not interfere," to 10, "completely interferes." Items were averaged to create an overall pain interference score for each diary. The BPI has been widely used in clinical populations and has demonstrated good responsiveness to changes in pain over time.[14,15]

Demographic and Clinical Variables

Age, biological sex, race, ethnicity, employment status, and household annual income were based on participant self-report. Disease status (suspected or definite CP) was provided by the treating physicians.

Alcohol use was ascertained using the Patient-Reported Outcomes Measurement Information System (PROMIS) v1.0 Alcohol Use—Short Form.[16] Participants were also asked where they experienced pain, including face, head, neck, shoulder, chest, abdomen/stomach, hand, arm, spine, lower back, pelvis, legs, and feet. Those experiencing pain in any other locations in addition to abdomen/stomach were classified as having nonabdominal pain. Participants also completed a questionnaire listing all medications they were currently taking, including opioids, nonopioid analgesics, and nonsteroidal anti-inflammatory drugs.

Psychosocial and Health-Related Quality of Life Measures

Participants completed the PROMIS-29 Profile v2.1 to assess pain interference, depression, anxiety, sleep disturbance, fatigue, physical function, and social function in the past 7 days. Good internal reliability and construct validity have been demonstrated in the general population as well as in populations with chronic pain.[17,18] T-scores were calculated such that a higher score indicated a higher level of the measure of interest (eg, a higher depression T-score for a higher level of depression, a higher physical function T-score for a higher level of physical function). Disease-specific health-related quality of life was assessed using the PANcreatitis Quality of Life Instrument (PANQOLI), an 18-item measure that was developed to evaluate quality of life in CP patients, which includes 4 subscales (physical function, role function, emotional function, and self-worth) and a total health-related quality of life score.[19] Strong reliability and construct validity have been demonstrated among adult CP patients.[19]

Statistical Methods

Calculating Indicators of Pain Magnitude, Variability, and Synchrony From Pain Diaries

The present analysis characterized dynamic pain experiences of CP patients captured within 7 days by using indicators of pain magnitude, pain variability, and pain synchrony derived from diary pain intensity measures. We excluded current pain intensity from analysis as it was less clinically meaningful, similar in value compared with average pain intensity, and subject to more variability due to the randomness of timing at the completion of diary. Therefore, only least pain intensity, worst pain intensity, and average pain intensity were used for analysis, constituting a total of 18 indicators (3 magnitude indicators, 12 variability indicators, and 3 synchrony indicators). We only included participants with 3 or more diaries completed, resulting in an analytic sample of 27 participants (90% of the full sample). Missing pain intensity diary data were imputed with pain intensity value reported in the last diary (last observation carried forward approach). For individual *pain magnitude*, we calculated the individual mean across 7 days for the items: least pain intensity, worst pain intensity, and average pain intensity.

The selection and calculation of intraindividual *pain variability* indicators were based on a methodology systematic review by Mun et al,[20] metrics used in statistics and medical literature for capturing individual variability, and a secondary analysis from the Pain in Sickle Cell Epidemiology Study.[11,20–22] Specifically, for each participant, we calculated individual coefficient of variation (CV) for the worst pain, least pain, and average pain intensity, respectively, as an indicator for overall pain variability across 7 days.[23] To account for temporal dependency, we also calculated autocorrelation at lag 1 [AR(1)] for each pain intensity measures across 7 days. A positive AR(1) indicated today's pain rating was more likely to be predicted by yesterday's pain rating (reflecting resistance to change), a negative AR(1) indicated a back-and-forth pattern of pain ratings, and an AR(1) closer to 0 indicated a lack of association between pain ratings at consecutive diaries.[20] To integrate both the magnitude of change and temporal dependency, we further calculated the root mean square of successive differences (RMSSD), which is a well-known variability metric.[24] In addition to the above statistical indicators of individual variability, we also calculated the probability of acute change (PAC) as indicating clinical pain variability.[20] Consistent with a previous study, we considered a change (either increase or decrease) in pain intensity scores of 2 or above as an acute change and calculated the probability of change for the worst, least, and average pain intensity across 7 days.[11]

We defined pain synchrony as the extent to which worst pain, least pain, and average pain were similar (for magnitude) or consistent (for correlation) with each other. Specifically, we calculated the difference between the worst pain and the average pain, as well as the difference between the average pain and the least

pain for each diary, and computed the 7-day individual mean of the worst-average difference and average-least difference. We also calculated the individual Spearman correlation coefficient between the worst pain and average pain across 7 days. Because of the high number of participants reporting 0 pain intensity for the least pain, individual correlation coefficients were not calculated between the least pain and the worst/average pain.

Identifying Distinct Patient Groups Using Pain Diary Indicators

K-means clustering was used to identify potential patient groups based on pain experience indicators calculated previously.[25] Principal component analysis (PCA) was used for reducing data dimensions (to reduce noise) before running the K-means clustering analysis.[26] The number of components were determined using the "proportion of variance accounted for" criterion so that the accumulated total variance explained by the retained components reached >80%.[27]

Before running the clustering analysis, we first determined clusterability (ie, whether there are potential clusters in the data) by checking the Hopkins statistic, with a value close to 1 indicating a high probability of clusters in the data (random data result in values around 0.5).[28] The number of clusters was determined by the "majority pick" based on a total of 30 statistical indices using the R program NbClust.[16] We then evaluated the internal validity of the identified clusters by examining cluster stability using the bootstrapping method (100 bootstrap sample pairs) that calculated the mean Jaccard similarity value (ranging 0–1).[29,30] A mean Jaccard similarity value of 0.75 or higher indicates a stable cluster (for each cluster).[31]

Comparing Patient Characteristics Across Identified Patient Groups

After identifying patient groups, we compared diary pain intensity indices (used for the clustering analysis), pain interference, and demographic (age and sex), clinical (disease stage, pain locations, analgesics), and psychosocial (PROMIS, PANQOLI) characteristics across groups. Categorical variables were compared using the chi-square tests or Fisher exact tests, and continuous variables were compared using the analysis of variance tests. Data management and statistical analyses were performed in R version 4.0.3.[32]

RESULTS

Participants included 30 subjects, with mean age of 49.8 years (standard deviation [SD], 12.5; range, 23–72), 80% women, and 87% non–Hispanic White (Table 1). Eighteen participants (60%) had definite CP and 12 (40%) had suspected CP. Twenty percent reported current use of alcohol. Most participants (73%) were using opioids for pain management. A total of 167 diary days were available for analysis; on average, participants completed 5.6 diary days. Clustering analysis was performed for the 27 participants (90% of the sample) with at least 3 diaries completed.

Distributions of the magnitude, variability, and synchrony indicators calculated from pain diaries are presented in Table 2. Overall, large variability was seen for these pain indicators according to the range values, suggesting heterogeneous pain experiences documented on pain diaries. The average pain intensity demonstrated the largest variability in CV (an indicator of overall magnitude of variability without accounting for temporal dependency), whereas the worst pain intensity demonstrated the largest variability according to RMSSD (an indicator integrating the magnitude of variability and time dependency) and PAC (an indicator of clinical meaningful variability). The difference between the worst and average pain intensity was slightly higher than the difference between the average and least pain intensity.

TABLE 1. Participant Characteristics (n = 30)

Characteristics	
Age, y	
Mean (SD)	49.8 (12.5)
Range	23–72
Sex, n (% women)	24 (80.0)
Race	
Black (eg, African, Haitian, Jamaican, Somali)	2 (6.7)
Chinese and Korean	1 (3.3)
South Asian (eg, Indian, Pakistani)	1 (3.3)
White (Caucasian)	26 (86.7)
Ethnicity, n (% Hispanic or Latino)	0
Marital status, n (%)	
Married	21 (70.0)
Divorced	5 (16.7)
Single	4 (13.3)
Employment status, n (%)	
Full time	10 (33.3)
Part time	6 (20.0)
Not working	14 (46.7)
Highest level of education completed, n (%)	
High school or less	3 (10.0)
Vocational or trade school	8 (26.7)
College or university	13 (43.3)
Graduate degree/professional school	6 (20.0)
Annual income, n (%)	
Less than $24,999	5 (16.7)
$25,000–$49,999	4 (13.3)
$50,000–$74,999	5 (16.7)
$75,000–$99,999	4 (13.3)
$100,000 and above	12 (40.0)
Pancreatitis diagnosis, n (%)	
Suspected CP	12 (40.0)
Definite CP	18 (60.0)
Psychiatric symptoms, n (% T-score ≥60)	
Depression	12 (40.0)
Anxiety	11 (36.7)
Sleep disturbance	14 (46.7)
Currently using alcohol, n (% yes)	6 (20.0)
Currently using opioid medication, n (% yes)	22 (73.3)

The Hopkins statistic was 0.949, indicating a very high probability of clusters in the data. Five components were retained according to the PCA analysis, which explained 86% of the total variance (the fifth component explained 7% of the variance). From the 30 statistical indices, the majority (6) proposed 4 as the best cluster number, and therefore, 4 was chosen as the optimal number of identified patient groups. As shown in Figure 1, 3 participants (11%) were classified into cluster 1, 4 (15%) into cluster 2, 9 (33%) into cluster 3, and 11 (41%) into cluster 4. Good cluster stability was shown by the clusterwise Jaccard bootstrap mean (0.73 for cluster 1, 0.86 for cluster 2, 0.81 for cluster 3, and 0.85 for cluster 4).

Comparing across the 4 clusters (Table 3), participants were differentiated mainly by pain magnitude and pain variability, and less by pain synchrony. Cluster 1 (11%) was characterized by minimal pain (lowest pain magnitude); the variability indicators were less meaningful in this group as participants reported low pain. Cluster 2 (15%) was characterized by moderate pain magnitude

TABLE 2. Distribution of Individual Pain Magnitude, Variability, and Synchrony Derived From 7-Day Online Daily Pain Diaries (n = 27)*

Indicators	Mean	SD	Minimum	Maximum
Mean of worst pain	5.28	2.03	0.57	8.14
Mean of least mean	2.80	1.65	0	5.71
Mean of average pain	3.84	1.84	0.14	6.43
CV of worst pain	0.32	0.27	0.05	1.05
CV of least pain	0.28	0.27	0	1.25
CV of average pain	0.42	0.55	0.08	2.65
AR(1) of worst pain	0.08	0.34	−0.78	0.56
AR(1) of least pain	0.08	0.26	−0.42	0.56
AR(1) of average pain	−0.02	0.32	−0.61	0.59
RMSSD of worst pain	1.49	0.87	0.41	3.24
RMSSD of least pain	0.82	0.65	0	2.27
RMSSD of average pain	1.15	0.58	0.41	2.52
PAC of worst pain†	0.31	0.29	0	1.00
PAC of least pain†	0.11	0.16	0	0.50
PAC of average pain†	0.19	0.23	0	0.83
Mean of worst-average pain difference	1.44	0.74	0.14	2.86
Mean of average-least pain difference	1.03	0.63	0	2.29
Correlation of worst pain and average pain	0.69	0.27	−0.08	0.99

*Indicators were calculated for the sample with at least 3 diaries available.

†Acute change indicates an increase or decrease of pain intensity by 2 or more points between consecutive days.

and high pain variability. Cluster 3 (33%) was characterized by moderate pain magnitude and low pain variability. Cluster 4 (41%) was characterized by the highest pain magnitude and lowest pain variability. Statistical comparisons were made for the 4 clusters. Statistically significant differences were found for the majority of the pain magnitude and variability indices. Pain interference (rated on pain diaries) was highest in cluster 4 and lowest in cluster 1, with statistically significant differences found between 4 clusters ($P = 0.017$).

Results regarding demographic, clinical, and psychosocial differences across the 4 clusters are presented in Table 4. Although few differences were statistically significant, patterns emerged. Specifically, from cluster 2 to cluster 4, age, female proportion,

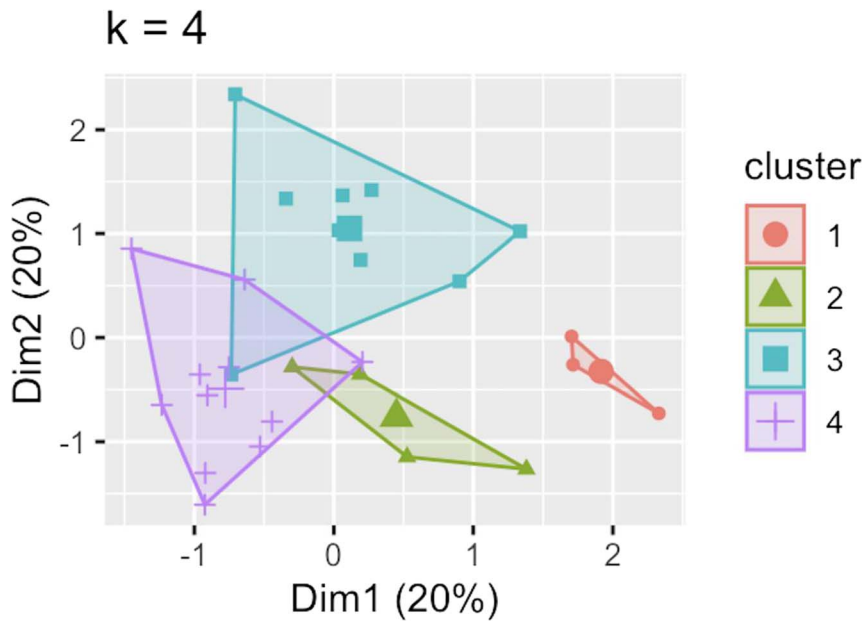

FIGURE 1. Identification of clusters using K-means clustering. Four clusters were separated by color boundaries. The larger red circle at the center of the red area indicates the center (ie, centroid) for participants in cluster 1, the larger green triangle at the center of the green area indicates the center for participants in cluster 2, the larger blue square at the center of the blue area indicates the center for participants in cluster 3, and the larger purple plus sign at the center of the purple area indicates the center for participants in cluster 4. Data points in each colored area were classified as belonging to each cluster. For the ease of visualization, figure portrays cluster separation on 2D dimensions.

TABLE 3. Pain Diary Characteristics Across Groups (n = 27)*

Diary Indicators	Group 1 (n = 3, 11%)	Group 2 (n = 4, 15%)	Group 3 (n = 9, 33%)	Group 4 (n = 11, 41%)	*P* for Difference†
Mean of worst pain	1.1	4.9	5.5	6.4	<0.001
Mean of least pain	0.1	2.9	2.0	4.2	<0.001
Mean of average pain	0.4	3.8	3.4	5.2	<0.001
CV of worst pain	0.92	0.37	0.30	0.14	<0.001
CV of least pain	0.42	0.55	0.30	0.13	0.034
CV of average pain	1.76	0.40	0.28	0.18	<0.001
AR(1) of worst pain	0.28	−0.14	−0.13	0.29	0.007
AR(1) of least pain	0.10	−0.11	0.02	0.19	0.19
AR(1) of average pain	−0.09	−0.30	0.01	0.09	0.23
RMSSD of worst pain	1.00	2.37	2.05	0.84	<0.001
RMSSD of least pain	0.19	2.08	0.78	0.57	<0.001
RMSSD of average pain	0.77	2.13	1.01	1.01	<0.001
PAC of worst pain	0.39	0.54	0.52	0.09	<0.001
PAC of least pain	0.00	0.42	0.07	0.06	<0.001
PAC of average pain	0.06	0.58	0.09	0.17	<0.001
Mean of worst-average pain difference	0.7	1.1	2.1	1.2	0.002
Mean of average-least pain difference	0.2	1.0	1.4	1.0	0.043
Correlation of worst pain and average pain	0.70	0.72	0.70	0.67	0.99
Mean of pain interference (diary)	0.22	3.86	3.50	4.80	0.017

*Clustering analysis was performed on the sample with at least 3 diaries available. Groups were derived from PCA, followed by K-means clustering based on mean of the worst pain, mean of the least pain, mean of the average pain, CV of the worst pain, CV of the least pain, CV of the average pain, AR(1) of the worst pain, AR(1) of the least pain, AR(1) of the average pain, RMSSD of the worst pain, RMSSD of the least pain, RMSSD of the average pain, PAC of the worst pain, PAC of the least pain, PAC of the average pain, mean of worst-average pain difference, mean of the average-least pain difference, and correlation of the worst pain and average pain. Truncation was made at 5 principal components, which explained 86% of the total variance.

†Differences across all 4 groups.

and the use of strong opioids increased; quality of life (PANQOLI) scores generally decreased (cluster 3 had the lowest scores for role functioning, self-worth, and the total score); PROMIS pain interference, fatigue, physical function, and social function domains generally worsened. Within clusters 2–4, cluster 3 had lower levels of depression and anxiety but the highest level of sleep disturbance.

DISCUSSION

This study presents a microlevel dynamic pain assessment method for patients with CP with the finding of 4 clusters with distinct pain patterns. The lack of clarity surrounding the mechanism of pain and its pathophysiology in CP makes it challenging to predict the type of pain patients will experience. As studies have shown, pancreatic morphology and disease duration have poor correlation with the pattern and severity of pain.[4,33,34] The treatment of pain represents a primary goal of managing the disease, but this becomes challenging for providers when pain patterns vary within and between patients. The identification of pain patterns could therefore guide the selection of specific treatment strategies and prove useful in both research and clinical settings.

Although several studies have attempted to expand upon the initial Ammann binary classification of pain in CP, one of the primary limitations has been the use of retrospective pain questionnaires to assess pain on an infrequent basis.[3,4,35,36] For example, in identifying pain patterns in the Dutch Chronic Pancreatitis Registry, pain questionnaires were sent once a year for follow-up upon enrollment, and in the NAPS2 study, retrospective review of patient records was used to assess pain.[4,36] In the Dutch study, more than half of patients changed pain patterns at least once during the follow-up period, which underscores the bias inherent to assessing pain over long retrospective reporting periods.[4] Therefore, in this study, we aimed to use daily pain diaries to more accurately capture the dynamic nature of pain in patients with CP.

One of the primary strengths of the daily BPI is the ability to capture the worst, average, and least amount of pain a person experiences during a given day, which can be used to track change in pain over time.[15] In this manner, we used various pain experience indicators to identify patient clusters, as opposed to simply categorizing patients as having "constant severe pain" or "intermittent pain." This resulted in the formation of 4 distinct patient clusters: (1) minimal pain, (2) moderate pain with high variability, (3) moderate pain with low variability, and (4) highest pain with lowest variability. Aside from the methodology of identifying these pain patterns, these are unique from previously reported pain patterns in that they quantify the variability with which pain is experienced on a day-to-day basis while also relaying the average amount of pain experienced during the day, enabling a microlevel assessment of pain.

In examining the differences between the 4 clusters, one of the most practical questions revolves around how quality of life differs between different pain clusters. Interestingly, although there was no significant difference between the clusters in overall score on the PANQOLI, the third cluster (moderate pain with low variability) had the worst quality of life. Although constant pain has been associated with worse quality of life in patients with CP, one would assume that the highest intensity pain would result in a lower quality of life.[3] Our results suggest that the steady presence of pain over most days impairs quality of life the most. In regard to the subscales, the third cluster also had the lowest scores in terms of role functioning and self-worth. Self-worth is a particularly unique measure of the PANQOLI, reflecting the stigmatization and financial

TABLE 4. Demographic, Clinical, and Psychosocial Characteristics Across Groups (n = 27)

	Group 1 (n = 3, 11%)	Group 2 (n = 4, 15%)	Group 3 (n = 9, 33%)	Group 4 (n = 11, 41%)	*P* for Difference*
Demographic variables					
Sex: female	2 (67%)	2 (50%)	7 (78%)	10 (91%)	0.32
Age: *M* (±SD)	44.8 (±15.4)	44.8 (±10.9)	48.4 (±13.9)	53.3 (±12.2)	0.60
Clinical variables					
Disease stage: definite CP	1 (33%)	4 (100%)	5 (56%)	6 (55%)	0.35
Pain locations: median (range)†	2 (1–2)	1 (1–3)	2 (1–6)	2 (1–5)	0.51
With any nonabdominal pain	2 (67%)	3 (75%)	6 (67%)	8 (73%)	1.00
Use of opioid medication	2 (67%)	3 (75%)	7 (78%)	8 (73%)	1.00
Analgesics intensity					0.83
Strong opioids	1 (33%)	2 (50%)	5 (56%)	8 (73%)	
Weak opioids	1 (33%)	1 (25%)	2 (22%)	1 (9%)	
Adjunct analgesics	1 (33%)	0	1 (11%)	1 (9%)	
Acetaminophen/NSAIDs	0	0	0	0	
None	0	1 (25%)	1 (11%)	1 (19%)	
Psychosocial variables					
Pancreatitis quality of life (PANQOLI)					
Total score	67.7	60.0	52.3	54.8	0.28
Physical function	23.3	18.5	16.0	16.0	0.14
Role functioning	13.7	15.3	13.4	14.3	0.91
Emotional function	13.3	12.0	10.9	10.8	0.78
Self-worth	17.3	14.3	12.0	13.6	0.40
PROMIS—pain interference	45.3	61.7	62.8	63.8	<0.001
PROMIS—physical function	57.0	43.8	43.0	40.9	0.032
PROMIS—fatigue	49.3	64.9	64.2	65.4	0.004
PROMIS—sleep disturbance	46.3	56.3	62.1	58.0	0.012
PROMIS—depression	51.0	56.8	53.9	58.1	0.64
PROMIS—anxiety	48.1	61.0	56.0	61.1	0.052
PROMIS—social function	56.5	43.6	42.4	42.9	0.004

NSAIDs indicates nonsteroidal anti-inflammatory drugs.

*Difference across all 4 groups.

†Pain locations include face, head, neck, shoulder, chest, abdomen/stomach, hand, arm, spine, lower back, pelvis, legs, feet, and other.

impact of the disease. As role function assesses the impact of CP on relationships including sexual activity and work activity, our findings may hint at the impact of low variability of pain, even at a moderate level of intensity, on the identity of the patient. Lastly, the first cluster (minimal pain) had the highest scores for overall quality of life and all the subscales, which reinforces the resilience that some patients demonstrate.

The PROMIS-29 instrument provides functioning and well-being data regarding 7 health domains, which can provide more granular data regarding patient experiences.[37] Data regarding the use of this instrument in patients with CP are lacking, and this study provides an initial glimpse into the relationship of pain patterns with specific health domains. Analogous to the PANQOLI, cluster 1 had the highest scores in terms of functioning and lowest scores for psychological health (depression and anxiety), again supporting the high influence of pain on CP-related health. Interestingly, sleep disturbance was worst in the third cluster and not in the fourth cluster, as would be expected given their high pain intensity. Notably, the second and fourth clusters both had anxiety scores >1 SD above the mean (general population), which may reflect the effects of high pain intensity and high pain variability. In addition, except for the first cluster, all clusters had high (>1 SD above the mean) fatigue scores, which represent a novel finding that likely represents the burden of pain in these patients. Nevertheless, further investigation is needed to explore how CP and pain contribute to fatigue in these patients, especially in combination with the malnutrition frequently seen in this disease.

The presence of a cohort of patients with minimal pain (first cluster) represents an interesting finding in light of the inclusion criteria for the study, which required participants to have experienced moderate (4 or higher on the 0–10 scale) pain intensity in the month before enrollment.[12] This likely reflects the natural course of the disease, where patients can have sporadic levels of pain day to day, and throughout each day. This highlights the limitation of prior studies where subjects are asked to quantify their pain on an annual basis, which will likely be affected by reporting biases.[38–40] This also speaks to the challenge of pain assessment performed during clinic visits, which is likely influenced by recent and salient experiences (eg, high recent pain exacerbation), and may potentially lead to inaccuracy in determining treatment choice and duration. We demonstrate the feasibility of daily electronic monitoring of pain via daily diaries in this patient population with acceptable levels of compliance.

Several limitations of this study warrant further discussion. The small sample size limits the ability to generalize these results, and caution is needed particularly in comparing the different pain

clusters. The small sample size also hinders the ability to generate well-defined pain clusters. In addition, although this study provides microlevel data, the results were limited to a 7-day pain diary completed once daily at the end of the day. As mentioned, the natural history of the disease likely results in changes in the pain experience, not only within each day but also over longer periods, which cannot be captured with 1 week of diaries alone. As pain assessment in CP will need to be comprehensive in nature, daily pain assessments may play an important role in describing the variability of pain on a microlevel. Future studies may incorporate ecological momentary assessment protocols to obtain pain ratings throughout the day to identify within-day variability. A large proportion of participants were also using opioids, which, although reflecting the management of CP in the United States, represent a potential confounder in identifying pain clusters. Our sample was also overrepresented by female participants, which can influence our results when considering that sex-related differences have been reported with regard to pain experiences.[41] About 40% of participants in our study had suspected CP who may have other conditions contributing to their pain; future studies should aim to recruit participants with confirmed CP. Lastly, in performing the analyses, we imputed data from the previous day's value for those with missing pain intensity scores. This conservative approach may reduce the overall pain variability, potentially affecting the validity of the identified clusters.

Similar to prior studies, we did not find any correlation with pain cluster and phenotypical findings or disease characteristics.[4,33] However, larger studies are needed to validate these findings with greater inclusion of racialized minorities. Further work is needed to identify whether these pain clusters represent distinct entities and whether these pain clusters have differential etiology, pain mechanisms, and clinical prognosis. For instance, associating pain clusters with potential biomarkers like electroencephalogram, pancreatic quantitative sensory testing, and functional magnetic resonance imaging could aid in understanding pain mechanisms and shaping treatment strategies. Importantly, as with all pain patterns in CP, prospective study is needed to determine ideal treatment regimens for each pain cluster. Longitudinal data will also help elucidate if and how these pain patterns may change over time, which can affect long-term management. Postsurgical pain patterns derived from pain diaries have been shown to predict recovery from surgery and pain in the pediatric population, and future work is needed to determine whether baseline pain patterns (as examined in this study) or posttherapy pain patterns can predict response to invasive treatment such as endotherapy and surgery in patients with CP.[42,43]

In summary, this study provides a first step in using daily pain diaries to capture the pain experience of patients with CP. Four distinct pain clusters accounting for daily pain variability and intensity were identified, and much work is needed for the validation of these findings. Nevertheless, microlevel pain assessments may enable the identification of distinct pain patterns that help identify treatment responders and nonresponders, which may ultimately aid the development of individualized treatment algorithms for patients with CP.

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