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Beyond Ammann's pain classification: multidimensional pain phenotyping and cluster analysis in chronic pancreatitis

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Abstract

Assessment of pain in chronic pancreatitis (CP) has largely focused on intensity and pattern, unable to address its complexity. To evaluate pain in a multidimensional fashion, we aimed to identify phenotypes based on the Comprehensive Pain Assessment Tool Short Form (COMPAT-SF) questionnaire and examine their associations with clinical factors. A cross-sectional study including 248 patients with painful CP from Asia, Europe, and the United States was performed. A cluster analysis including the 5 pain dimensions from the COMPAT-SF questionnaire (severity, fluctuation, provocative factors, spreading pain, and qualitative descriptors) identified pain phenotypes. The phenotypes were compared to demographic and clinical data, including patient-reported outcomes and quantitative sensory testing. Three phenotypes were identified in the cluster analysis: a low-burden phenotype, cluster 1 (n = 151); a high-intensity, constant pain phenotype, cluster 2 (n = 75); and a widespread pain, multidimensional phenotype, cluster 3 (n = 22). Quality of life and sleep scores were worse in cluster 3 than in the other phenotypes (all $P < 0.001$). The degree of anxiety, depression, and catastrophizing was also worse in cluster 3 (all $P < 0.001$). Cluster 3 showed increased hyperalgesia on sensory testing with a lower sum of pressure pain detection thresholds than cluster 1 ($P = 0.008$) and higher temporal summation than cluster 2 ($P = 0.023$). The COMPAT-SF questionnaire thereby identified 3 clinically relevant phenotypes in CP. Widespread, multidimensional pain correlated with increased hyperalgesia, higher psychological distress, and worse overall well-being. Phenotyping based on the COMPAT-SF questionnaire may prove helpful in guiding treatment plans and more accurately allocating patients in clinical trials.

Keywords: Chronic pancreatitis, PAIN, Cluster analysis, Pain measurement, Quality of life

1. Introduction

Despite its frequency and burden, pain in chronic pancreatitis (CP) remains poorly understood. Chronic pancreatitis-related pain is not a homogeneous entity. It can vary widely in terms of location, character, timing, intensity, quality, and response to treatment.[7,25] The heterogeneity likely reflects differences in underlying pain mechanisms, including nociceptive input from the gland tissue, neuropathic pain because of nerve damage, neuroplastic changes, and psychosocial factors.[33]

Pain management strategies in the literature often reflect a "one-size-fits-all" approach that fails to address the individual variations in symptom burden and pain mechanisms. Pain assessment has, until now, focused primarily on pain intensity and pattern, often relying on nonspecific or nonvalidated instruments.[40] In recent years, the Comprehensive Pain Assessment Tool Short Form (COMPAT-SF), a multidimensional, CP-specific pain assessment tool, has shown increasing promise. It captures 5 key dimensions of pain experience: intensity, fluctuation,

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provoking factors, spreading, and qualitative descriptors, and shows promise as a sensitive marker in clinical studies.[16,26]

Pain phenotyping has shown promise in other chronic pain conditions, as a means of evaluating pathophysiology, guiding treatment selection, and improving outcomes.[3] In CP, pain phenotyping has primarily focused on quantitative sensory testing (QST), and its clinical availability is limited.[10] We hypothesize that pain phenotypes can be identified in patients with CP based on patient-reported outcomes (PROMs). These phenotypes are thought to differ in clinical characteristics, psychological burden, and quality-of-life. We, therefore, aim to apply a data-driven approach to identify CP phenotypes based on the dimensions from COMPAT-SF. These phenotypes will be compared across variables, including quality of life, sleep quality, psychosocial burden, response to nociceptive stimuli, and endogenous pain modulation, in alignment with the IMMPACT recommendations for pain phenotyping.[9] This approach can contribute to a more detailed understanding of CP-related pain and support future efforts toward mechanism-based pain management.

2. Methods

2.1. Study design and population

This is a cross-sectional multicenter study based on data from the INPAIN (Individualized PAIN phenotyping in chronic pancreatitis) study. The study followed a predefined protocol.[17]

Inclusion criteria were as follows: definite CP diagnosed by the MANNHEIM criteria,[38] chronic abdominal pain (pain ≥3 days per week for ≥3 months),[21,23,32] and age of ≥18. Exclusion criteria were previous major abdominal surgery (besides pancreatic surgery), where scars and nerve lesions can interfere with the QST procedures, and severe pain of other etiologies than CP.

2.2. Outcome measures

This part of the study was designed to examine the interplay between results from the COMPAT-SF questionnaire and other PROMs, as well as demographic parameters and QST. Data from all patients with current painful CP were used in the analysis. The COMPAT-SF questionnaire dimensions are shown in supplemental digital content (see Table S1, http://links.lww.com/PAIN/C403).

The data included in this study consisted of patient and disease characteristics, including age, sex, disease duration, BMI, comorbidities, presence of exocrine (fecal elastase <200 μg/g and signs of malabsorption) and endocrine insufficiency (hemoglobin A 1c ≥ 48 mmol/mol), whether they have had previous pancreatic surgery, information on alcohol abuse (>10 standard units of alcohol per week), analgesic treatment (opioids/adjuvant analgesics), active or previous tobacco use, and TIGAR-O risk factors.[41] The relationship between COMPAT-SF scores and morphological features was not examined because of lack of temporal alignment between scans and the completion of PROMs. The following PROMs were used: COMPAT-SF,[26] the Pain Catastrophizing Scale,[36] the European Organization For Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30),[11] Hospital Anxiety and Depression Scale,[4] and the Pittsburgh Sleep Quality Index.[5] Quantitative sensory testing consisted of 4 measurements (see Table S2, supplemental digital content, http://links.lww.com/PAIN/C403).[37] For details on the questionnaires, including methods for evaluation, please see supplementary methods as well as relevant references.[4,5,11,26,36]

Follow-up visits were planned at 3 months after baseline, 6 months, 12 months, 18 months, and 24 months. As it is an ongoing study, not all patients had completed the follow-up visits. At follow-up, patients were asked to complete the PROMs mentioned above, as well as the Patient-reported Global Impression of Change (PGIC).

2.3. Statistical analysis

A principal component analysis (PCA) was performed on the COMPAT-SF dimensions to determine which dimensions to include in the cluster analysis. An unsupervised cluster analysis was conducted using the relevant dimensions to identify phenotypes. All dimension scores were Z-score normalized before clustering. Hierarchical clustering (complete linkage) was used because of the presence of one binary dimension and 4 numeric dimensions. Clustering validity was evaluated using generalized silhouette width and compared with PCAmix-based clustering. The cluster analysis was repeated in 2 subgroups (Asian patients and European/American patients) and compared to secure similar patterns. For external validation, the cluster analysis was repeated in an independent dataset from a prior study, including 135 unique patients,[26] to evaluate cluster comparability.

After cluster formation, the COMPAT-SF dimensions were compared between phenotypes using one-way analysis of variances (ANOVAs) with robust standard errors. Patient-reported outcomes, clinical, and demographic variables were compared between phenotypes using either ANOVA for continuous variables or chi-squared tests for categorical variables. To inform threshold selection for a rule-based classification model, we fitted a multinomial logistic regression model using the pain dimension scores. In a supervised derivation step, we trained a CART decision tree to reproduce the 3 clusters from the 5 COMPAT-SF dimensions using a stratified 80/20 split. The performance of the rule-based approach was evaluated against the original cluster assignment using a confusion matrix. Last, the validity was further examined in the external dataset using a confusion matrix and calculating the Adjusted Rand Index (ARI).

Statistical analyses were performed using R version 4.5.0 (R Core Team, Vienna, Austria) and RStudio version 2025.05.0 (Posit Software, Boston, MA). To account for multiple comparisons, *P*-values were Benjamini–Hochberg adjusted. Complete case analysis was applied. Statistical significance was set at a 2-sided *P*-value <0.05.

3. Results

3.1. Patient characteristics and dimensionality of pain

Baseline data from 248 patients (65% males) with a mean age of 42.2 years were included in the study. Because of ongoing inclusion, follow-up data were only available for 130 patients on 3-month follow-up, 103 at 6-month follow-up, 59 at 12-month follow-up, and 24 at 18-month follow-up. No patients had completed the 24-month follow-up at time of analysis. The median follow-up time was 3 months (IQR 0-12).

The principal component analysis revealed that the first principal component explained 47.8% of the total variance, with all 5 variables loading highly and relatively equally on this component (loadings ranging from 0.34 to 0.51), indicating a shared underlying construct of pain (**Fig. 1**). Notably, the pain spreading and the pain provocation dimensions also showed strong loadings on the second component (0.33-0.35),

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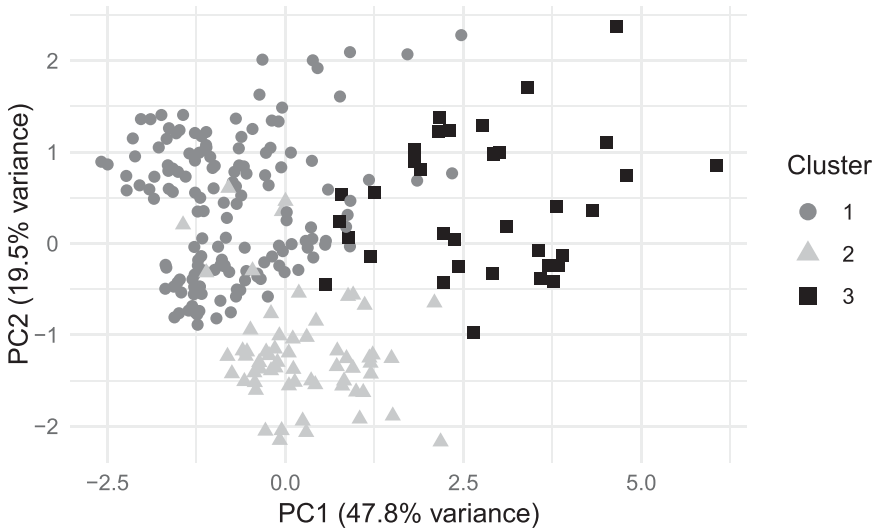

Figure 1. Principal component analysis of COMPAT-SF dimensions across pain clusters. Principal component analysis (PCA) based on the 5 COMPAT-SF pain dimensions. Each point represents a single patient, colored according to cluster membership.

suggesting that these capture a partially independent pain dimension. Although the first principal component suggested a common general pain burden, the second principal component captured additional structures, particularly in spreading and provocation, so we retained all 5 dimensions, instead of combining them into the total score, to preserve clinically relevant heterogeneity.

3.2. Cluster identification, internal, and external validation

Using hierarchical clustering on the 5 COMPAT-SF dimensions, we selected a 3-cluster solution because it demonstrated good internal validity (mean silhouette >0.5) and high reproducibility across alternative clustering strategies (92% concordance between Gower- and PCAmix-based clustering). In contrast, a 2-cluster solution showed lower silhouette values, poorer reproducibility, and merged clinically distinct groups, whereas a 4-cluster solution reduced silhouette scores and reproducibility. Together, these findings support 3 clusters as the most clinically meaningful representation of the underlying pain profiles[10] (**Fig. 2**).

The hierarchical cluster analysis defined 3 separate phenotypes (**Table 1**). The phenotypes were named based on their main COMPAT-SF results. Cluster 1: low-burden phenotype; cluster 2: high-intensity, constant pain phenotype; and cluster 3: widespread, multidimensional pain phenotype (**Fig. 3**).

The cluster analysis was repeated in 2 subparts of the patient population: the Asian patients (n = 149) and the European/American patients (n = 97). The results showed similar cluster formations (see Table 3, supplemental digital content, http://links.lww.com/PAIN/C403). However, the distribution varied geographically, with cluster 3 being less prevalent in Asia than in Europe/the United States ($P < 0.001$) (**Fig. 4**). Details on the geographically clusters are presented in supplemental digital content (see Tables 3–4, http://links.lww.com/PAIN/C403).

External validation in an independent dataset (n = 135) supported a comparable three-cluster solution, with consistent profiles for cluster 1 (low-severity) and cluster 3 (widespread and multidimensional). Cluster 2 (intermediate) was less represented (n = 6, 4%) compared to the original cohort (n = 75, 30%) (see Table S5, supplemental digital content, http://links.lww.com/PAIN/C403).

Figure 2. Generalized silhouette width for each phenotype. Silhouette widths are plotted for all individual observations ordered within each cluster. Positive values indicate good cohesion and separation, whereas negative values suggest potential misclassification. The mean generalized silhouette width for the model was 0.52, indicating moderate cluster separation. The majority of observations show positive silhouette values, indicating moderate internal consistency and distinctiveness across the 3 identified phenotypes.

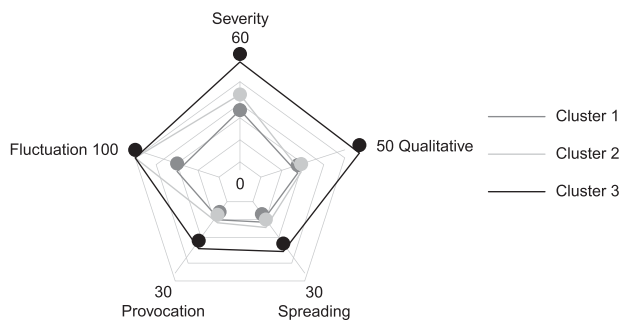

Figure 3. COMPAT-SF phenotype profiles. The figure illustrates the average scores across the 5 COMPAT-SF dimensions for each phenotype. The range of each dimension has been adapted to the values measured. Fluctuation score = 50 equals intermittent pain, 100 equals constant pain. The colored lines represent the phenotypes.

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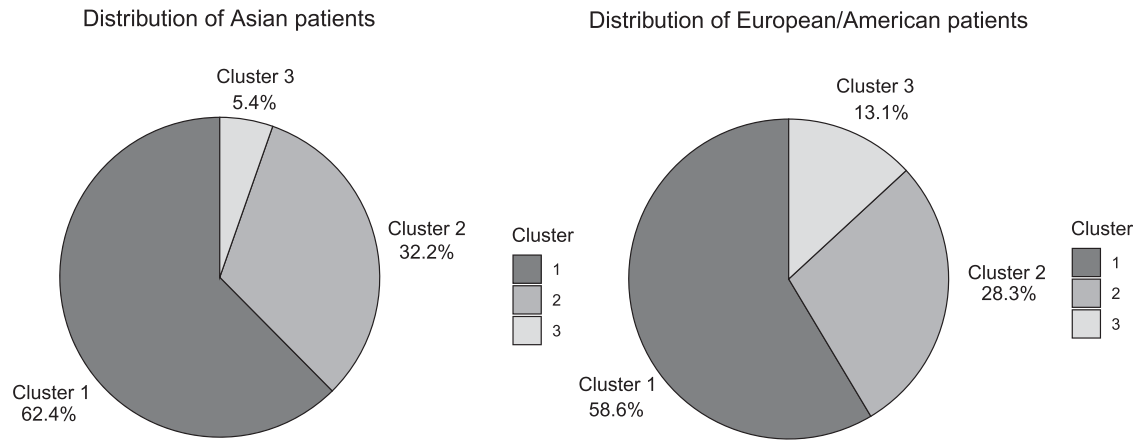

Figure 4. Phenotype distribution by geographic region. The relative distribution of patients across the 3 identified phenotypes stratified by region.

3.3. Comparison across phenotypes

The demographic comparison (**Table 1**) showed that patients in the widespread, multidimensional pain phenotype had higher BMI ($P = 0.006$) and increased alcohol ($P = 0.002$). More patients with this phenotype used adjuvant analgesics ($P < 0.001$). The number of patients using opioids increased throughout the clusters ($P = 0.001$).

Differences in COMPAT-SF dimension scores were observed across all phenotypes (all $P < 0.001$) (**Table 1** and **Fig. 5**).

The widespread, multidimensional phenotype had worse quality of life and sleep than the other phenotypes (both $P < 0.001$). Similarly, anxiety scores were worse in this phenotype than in the other 2 phenotypes (both $P < 0.001$). Catastrophizing and depression also increased progressively between phenotypes, with higher scores in the widespread, multidimensional pain phenotype (all $P < 0.001$) (**Fig. 6**).

Quantitative sensory testing results differed between phenotypes, with the widespread, multidimensional pain phenotype being the most pathological. Hence, the pressure pain detection threshold sum was lower in this phenotype than in the low-burden phenotype ($P = 0.008$) (**Table 2**).

Temporal summation at the forearm (reflecting high neuronal excitability) was increased in the widespread, multidimensional pain phenotype compared with the high-severity, constant pain phenotype ($P = 0.024$).

3.4. Rule-based cluster classification model

The learned tree from the supervised CART decision tree training yielded concise rules (**Fig. 7**):

(1) If pain fluctuation = intermittent → cluster 1.

(2) Else:

- If provocation score < 13.75 and qualitative score < 58.7 → cluster 2.
- If provocation score < 13.75 and qualitative score ≥ 58.7 → cluster 3.
- If provocation score ≥ 13.75 and severity score < 53.3 → cluster 2
- If provocation score ≥ 13.75 and severity score ≥ 53.3 → cluster 3

On the training set, accuracy was 0.985 (95% CI, 0.957-0.997), and on the held-out test set, accuracy was 1.00 (95% CI, 0.928-1.000). Variable importance indicated pain fluctuation as

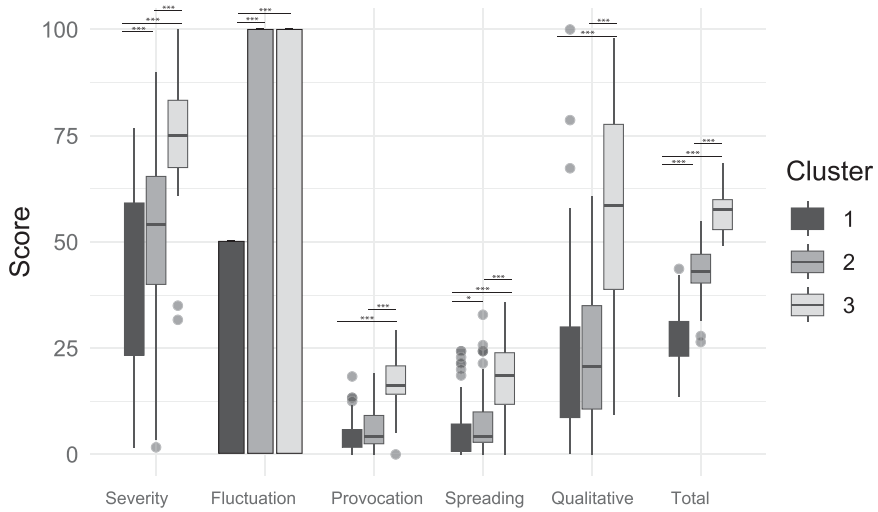

Figure 5. Mean COMPAT-SF scores across phenotypes. The bar plot displays mean scores for each of the 5 COMPAT-SF pain dimensions, as well as the total score, stratified by phenotype. Asterisks indicate significance levels (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

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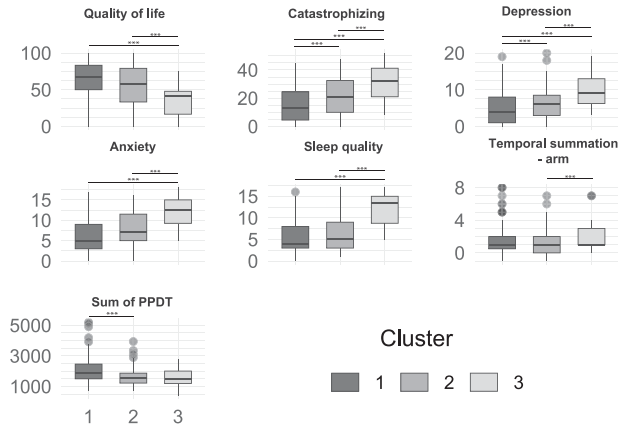

Figure 6. Patient-reported outcomes across phenotypes. Bar plots show mean scores for various PROMs stratified by phenotype. Asterisks indicate significance levels (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

the dominant split, followed by provocation score, severity score, qualitative score, and spreading score.

When examining the accuracy in the external dataset, it had an accuracy of 90% (95% CI, 0.841-0.948), and an ARI = 0.818 (confusion matrices in Table S6, supplemental digital content, http://links.lww.com/PAIN/C403).

3.5. Cluster variance over time

Using the clusters derived from the baseline analysis and a classification of follow-up data based on the rule-based classification model, we examined patient cluster movement throughout follow-up. Overall stability from baseline to 3-month follow-up was 73.1% (95/130). Stepwise stability increased at later comparisons (restricted to complete pairs): 87.4% for 3- to 6-month follow-up, 91.5% for 6- to 12-month follow-up, and 91.7% for 12- to 18-month follow-up. The distribution of PGIC differed significantly across cluster transitions ($\chi^2(10) = 32.8$, $P < 0.001$) at the 3-month follow-up. Patients classified as "improved" by cluster shift tended to report PGIC categories of "much" or "minimally improved," whereas patients with worsening cluster assignment reported poorer PGIC. However, the ordinal correlation between the 2 scales was weak and nonsignificant (Spearman $\rho = -0.11$, $P = 0.21$). A Sankey plot depicting the movements is shown in **Figure 8**.

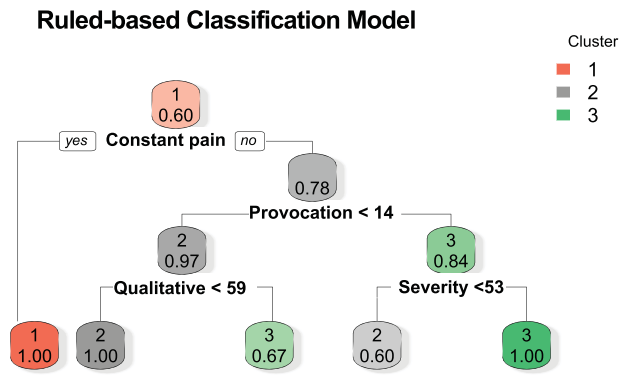

Figure 7. Rule-based classification of phenotypes. Flowchart illustrating the rule-based algorithm used to classify patients into the 3 phenotypes (clusters).

4. Discussion

Cluster analysis identified 3 phenotypes from the COMPAT-SF. These phenotypes showed meaningful differences in patient-reported outcomes, clinical characteristics, and sensory measures, with the widespread, multidimensional pain phenotype having the most impact on the clinical presentation. The cluster formation was validated across continents through subgroup analysis and in an external dataset. There was a moderate internal consistency in the cluster solution, comparable with scores from other studies that phenotyped chronic pain patients through cluster analysis.[8]

Previous efforts to characterize pain in CP have recognized the heterogeneity in pain experience and its clinical significance. The longitudinal studies by Ammann et al. distinguished between intermittent and continuous pain trajectories and demonstrated the relevance of pain patterns to disease progression and outcomes.[2] This founded subsequent work, including large-scale observational cohorts such as NAPS2, which showed that constant pain is associated with greater disability, opioid use, and reduced quality of life.[30] Prior research has similarly highlighted the value of pain pattern subtypes in understanding clinical burden and treatment needs.[10] However, these classifications may not reflect the full multidimensional complexity. The current study used data-driven clustering based on validated multidimensional pain assessment and compared the phenotypes on psychophysical and psychological profiling. While confirming Ammann's observations, the model offers an additional understanding by integrating additional pain dimensions. Importantly, differences in methodology and populations, such as chart review vs patient-reported outcomes, varying observation windows, and Ammann's predominantly alcoholic CP cohort compared with our broader sample, mean that the phenotypes are not directly equivalent. We, therefore, consider the parallels as contextual rather than confirmatory and interpret divergences with caution.

4.1. External cluster validation

In the external dataset, the overall three-cluster structure was reproduced. The main divergence was that cluster 2 was markedly smaller and had lower severity scores than in the original cohort, likely reflecting sample variability and reduced statistical stability in this subgroup. Notably, the rule-based classification system achieved a high ARI when applied to this dataset, indicating strong concordance between model-based predictions and unsupervised clustering. These findings suggest that the clusters are reproducible at the individual patient level, although relative cluster sizes varied between cohorts. The robustness of cluster 1 and cluster 3 across cohorts supports their validity as distinct subgroups. By contrast, the intermediate cluster appears more sample-sensitive, which is consistent with its conceptual role as a transitional phenotype bridging the 2 extremes.

4.2. Phenotypes and demographics

The phenotypes differed in demographics in terms of BMI and continued use of alcohol. The widespread, multidimensional pain phenotype had a higher frequency of active alcohol abuse. Similarly, smoking was more frequent in patients with this phenotype, although not significantly. Both alcohol and smoking have been linked with severe pain in previous studies.[34] The increased BMI in the widespread, multidimensional phenotype seems counterintuitive, as previous studies have shown that underweight is related to an increased occurrence of pain in

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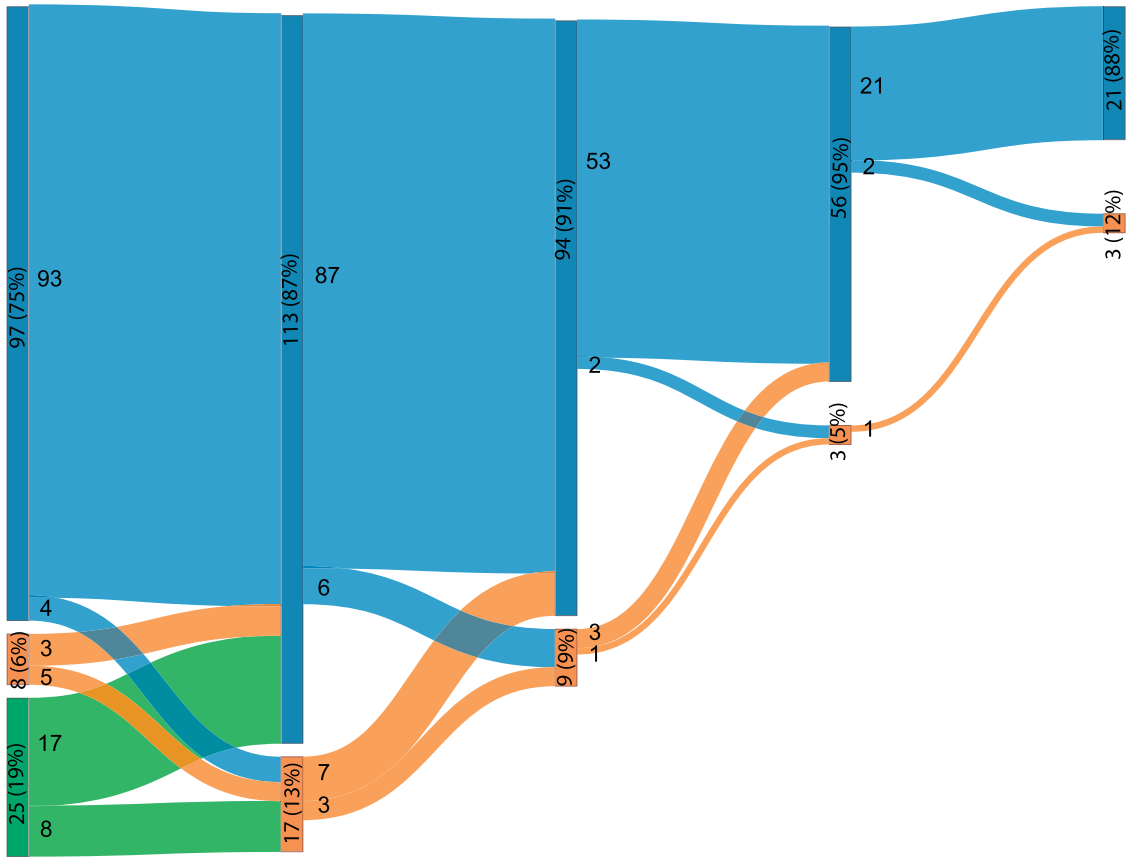

Figure 8. Cluster variance over time. A Sankey plot illustrating how clusters vary over time. The follow-up clusters are based on the rule-based classification system as described. Blue equals cluster 2, orange cluster 2, and green cluster 3.

CP.[31] However, another study has found that being overweight is associated with alcoholic CP, and the increased BMI might, therefore, be an innocent bystander.[1] However, a recent meta-analysis has shown that excess fat and obesity in general are associated with higher pain intensity and, therefore, might play a part in CP-related pain and pain perception.[13]

The opioid use increased throughout the pain phenotypes, with the highest use in the widespread, multidimensional phenotype. Similarly, the use of adjuvant analgesics was more frequent in the widespread, multidimensional phenotype than in the others. This may reflect a shift toward the search for an opioid-sparing strategy, with increased use of adjuvant analgesics when a psychological component is suspected.[24]

We observed notable geographical differences in phenotype distribution. The widespread, multidimensional pain phenotype was rarely seen in Asian patients, whereas the prevalence in European and American patients was almost 4 times as high. This phenotype was associated with pancreatic injury linked to alcohol and obesity, reflecting underlying inflammatory and metabolic stressors. Notably, these risk factors are less prevalent in the included parts of Asia than in the Western countries.[12,15,22,28,29] Cultural differences and healthcare access may further explain these patterns. Pain perception and reporting are shaped by cultural norms, with some populations more likely to underreport or normalize symptoms. In addition, opioid-based treatments are less prevalent in India than in Western countries, where antidepressants and other alternatives may be favored. Such approaches could limit affective dimensions of pain that contribute to the widespread, multidimensional pain phenotype.[6]

4.3. Pain phenotypes and patient-reported outcomes

The widespread, multidimensional pain phenotype demonstrated the worst scores in all PROMs, including quality of life. Other studies also associate quality of life with pain severity.[30,35] This indicates that widespread and multidimensional pain represents a more severe type of pain than can be indicated solely from pain intensity and pattern. Similarly, catastrophizing was more prevalent in the widespread, multidimensional phenotype, aligning with previous research.[39] Symptoms of depression and anxiety were also more prevalent in the widespread, multidimensional phenotype. The association between psychological distress and pain severity has been documented across various chronic pain populations.[18] The increased affection of sleep quality in the widespread, multidimensional phenotype is comparable to findings from other studies.[19] These results validate the phenotypes and suggest that they represent clinically meaningful entities reflecting pain severity.

4.4. Pain phenotypes and quantitative sensory testing

The low-burden pain patients have relatively preserved pain processing compared with patients experiencing high-severity pain. The widespread, multidimensional pain phenotype demonstrated pronounced temporal summation at the forearm, suggesting a heightened neuronal excitability. Temporal summation is typically associated with continuous nociceptive drive and is one of the most robust measures indicating central sensitization.[27] The widespread, multidimensional phenotype both had increased temporal summation alongside a high

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Table 1

Demographic and COMPAT-SF characteristics.

	Cluster 1: low-burden phenotype	Cluster 2: high-intensity, constant pain phenotype	Cluster 3: Widespread, multidimensional phenotype	p-value	Post-hoc	Missing data, %
N	151 (60.9%)	75 (30.2%)	22 (8.9%)			
Female sex	46 (30.5%)	32 (42.7%)	8 (36.4%)	0.190		0.0
Age, y	43.0 (14.3)	39.6 (15.8)	45.6 (13.7)	0.147		0.4
Disease duration, y	6.2 (6.9)	7.6 (6.9)	5.1 (5.0)	0.219		1.6
BMI, kg/m^2	22.3 (5.9)	22.8 (5.5)	27.4 (14.6)	**0.006**	**b, c**	0.0
Age-adjusted CCI	1.2 (1.6)	1.1 (1.5)	1.6 (1.5)	0.539		0.0
Alcohol abuse	45 (29.8%)	14 (18.7%)	14 (63.6%)	**0.002**	**a, b, c**	0.4
Diabetes	50 (33.1%)	29 (38.7%)	9 (40.9%)	0.611		0.0
Exocrine insufficiency	67 (44.4%)	38 (50.7%)	10 (45.5%)	0.668		0.0
Previous pancreatic surgery	15 (9.9%)	10 (13.3%)	4 (18.2%)	0.462		0.0
Previous endoscopies	43 (28.5%)	20 (26.7%)	7 (31.8%)	0.889		0.0
Analgesic treatment						
Opioids	75 (49.7%)	46 (61.3%)	20 (90.9%)	**0.001**	**a, c**	0.0
Adjuvants	3 (2.0%)	7 (9.3%)	7 (31.8%)	**<0.001**	**a, b**	0.0
Smoking				0.066		0.0
Never	81 (53.6%)	47 (62.7%)	6 (27.3%)			
Past	33 (21.9%)	14 (18.7%)	7 (31.8%)			
Current	37 (24.5%)	14 (18.7%)	9 (40.9%)			
Risk factors (TIGAR-O)				**0.004**	**a, b**	0.0
Alcohol	52 (34.4%)	13 (17.3%)	14 (63.6%)			
Idiopathic	73 (48.3%)	49 (65.3%)	7 (31.8%)			
Other	26 (17.2%)	13 (17.3%)	1 (4.5%)			
COMPAT-SF scores						0.0
Severity score	40.7 (20)	51.3 (18.9)	73.5 (16.4)	**<0.001**	**a, b, c**	
Fluctuation score = constant	0 (0%)	61 (100%)	36 (100%)	**<0.001**	**a, b**	
Provocative score	4.3 (3.5)	5.5 (4.5)	16.4 (6.9)	**<0.001**	**b, c**	
Spreading score	5.2 (5.4)	7.5 (7.4)	17.6 (10.6)	**<0.001**	**a, b, c**	
Qualitative score	22.0 (16.6)	24.0 (16.7)	58.8 (24.3)	**<0.001**	**b, c**	
Total score	27.1 (6.2)	43.1 (5.3)	57.0 (4.9)	**<0.001**	**a, b, c**	

Demographical data and COMPAT-SF scores in the 3 phenotypes. All data are presented as mean (SD) or n (%) as appropriate.

*Post-hoc analysis: a = cluster 1 is different from cluster 2; b = cluster 1 is different from cluster 3; c = cluster 2 is different from cluster 3.

BMI, body mass index; CCI, Charlson comorbidity index.

COMPAT-SF spreading score, making it plausible that it represents central sensitization.

4.5. Rule-based cluster classification model

To facilitate a practical application, a simplified rule-based model was developed to classify patients into pain clusters. The model demonstrated excellent performance for all phenotypes. When testing the rule-based classification model on the external dataset, it yielded a substantial accuracy, indicating that it is clinically useable beyond the original dataset.

4.6. Cluster variance over time

Patients shifted between clusters during follow-up, with a tendency toward improvement, especially at the early visits. Several mechanisms may explain this pattern. First, fluctuations in pain severity are common in chronic pancreatitis, and changes may reflect natural variation over time.[20] Second, improvements may be attributable to treatment effects, as a proportion of patients in the INPAIN study initiated new therapies during follow-up. Finally, one cannot exclude nonspecific effects of study participation itself, such as increased clinical attention, which can influence patient-reported outcomes.[14] The PGIC responses differed across cluster-change groups, suggesting that patients who improved or worsened in cluster assignment tended to report corresponding global impressions of change. However, the absence of significant correlation shows that this relationship is not uniform. Therefore, patient-reported improvements did not increase in a simple linear fashion with "improving" cluster shifts, nor did reported worsening align consistently with "worsening" shifts.

4.7. Strengths and limitations

The strengths include the multinational design. The design enhances the generalizability of the phenotypes across geographic regions, and an external validation strengthens the results. The sample size increases the clinical applicability and robustness of findings. Notably, the identification of data-driven phenotypes provides a valuable foundation for a personalized approach. The cluster formation was relatively independent of geography, further strengthening the results.

However, some limitations should be noted. The cross-sectional design precludes causal interference regarding

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Table 2

Phenotype characteristics.

	Cluster 1: low-burden phenotype	Cluster 2: high-intensity, constant pain phenotype	Cluster 3: widespread, multidimensional phenotype	p-value	Post-hoc	Missing data, %
Questionnaires						
Quality of life	65.3 (25.3)	56.9 (23.7)	34.1 (20.4)	**<0.001**	**b, c**	0.0
Catastrophizing	15.2 (12.5)	21.6 (12.6)	31.5 (12.5)	**<0.001**	**a, b, c**	0.0
Anxiety	5.8 (4.2)	7.6 (4.3)	12.0 (3.4)	**<0.001**	**a, b, c**	0.0
Depression	5.0 (4.5)	6.4 (4.5)	9.8 (4.3)	**<0.001**	**b, c**	0.0
Sleep quality (PSQI)	5.5 (3.7)	6.2 (3.8)	12.1 (4.0)	**<0.001**	**b, c**	6.9
QST						
PPDT C5, kPa	363.7 (167.7)	313.5 (134.8)	294.1 (99.4)	0.167		0.0
PPDT TH10 dorsum, kPa	497.9 (244.8)	374.7 (160.8)	390.4 (191.1)	**0.006**	**a**	0.0
PPDT TH10 abdomen, kPa	284.8 (141.1)	242.3 (108.4)	219.9 (136.4)	0.143		0.0
PPDT L1, kPa	329.1 (140.8)	304.0 (117.3)	273.4 (132.1)	0.202		0.0
PPDT L4, kPa	571.7 (299.8)	407.7 (166.1)	421.3 (155.2)	**0.002**	**a, b**	0.0
TS abdomen	1.8 (1.6)	1.6 (1.9)	1.2 (1.5)	0.539		0.0
TS arm	1.7 (1.7)	1.3 (1.6)	2.0 (2.1)	**0.023**	**c**	0.0
CPM relative, %	3.7 (21.4)	6.1 (16.1)	11.2 (21.6)	0.163		0.0
CPM absolute, kPa	13.5 (143.0)	28.9 (88.2)	56.8 (128.4)	0.364		0.0
PPDT index	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)	0.577		0.0
PPDT sum, kPa	2047.1 (834.7)	1642.3 (596.5)	1599.1 (626.7)	**0.008**	**a**	0.0

Phenotype evaluation, based on patient-reported outcome measures and QST evaluations. Analyses were adjusted for potential confounders: age, sex, disease duration, analgesic treatment, and comorbidity index.
*Post-hoc analysis: a = cluster 1 is different from cluster 2; b = cluster 1 is different from cluster 3; c = cluster 2 is different from cluster 3.
PSQI, Pittsburgh sleep quality index; QST, quantitative sensory testing; PPDT, pressure pain detection threshold; CPM, conditioned pain modulation; TS, temporal summation.

mechanisms underlying phenotype differences. Modest cluster separation and residual between-group differences in comorbidity and health behavior may also introduce bias.

4.8. Clinical and research implications

Although preliminary, these phenotypes suggest that individual clusters based on a questionnaire that can be completed in less than 10 minutes may reflect underlying mechanisms and may respond differently to targeted interventions. For instance, patients with the high-intensity, constant pain phenotype might benefit from neuromodulating pharmacological treatments or spinal interventions. In contrast, those with the widespread, multidimensional pain phenotype may require a multimodal approach involving psychological support, physical rehabilitation, and strategies targeting central pain modulation.

From a research perspective, this classification has the potential to inform future clinical trial design. Cluster-based stratification could be valuable in early-phase trials, where enrolling a homogeneous subgroup may increase the likelihood of detecting treatment effects. In later-phase trials, broader inclusion remains relevant, but sensitivity analyses based on cluster affiliation may reveal differential treatment responses and help refine subgroup-specific indications.

5. Conclusions

This study identified 3 phenotypes in patients with CP based on a multidimensional assessment of pain using the COMPAT-SF questionnaire and provides a simple, clinically applicable scoring algorithm. The phenotypes included a low-burden pain phenotype, a constant, high-intensity pain phenotype, and a widespread, multidimensional pain phenotype. The phenotypes differed meaningfully in psychological burden, sensory function, and pain modulation, supporting the relevance of patient-reported pain profiles for phenotyping. These findings emphasize the heterogeneity of CP pain experience and may offer a valuable step towards personalized assessment and treatment strategies. In addition, the identified phenotypes may support patient stratification in clinical trials. However, longitudinal studies are needed to validate stability and predictive value.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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