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Identifying patient subgroups in the heterogeneous chronic pain population using cluster analysis

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ABSTRACT

Chronic pain is an ill-defined disease with complex biopsychosocial aspects, posing treatment challenges. We hypothesized that treatment failure results, at least partly, from limited understanding of diverse patient subgroups. We aimed to identify subgroups using psychological variables, allowing for more tailored interventions. In a retrospective cohort study, we extracted patient-reported data from two Dutch tertiary multidisciplinary outpatient pain clinics (2018–2023) for unsupervised hierarchical clustering. Clusters were defined by anxiety, depression, pain catastrophizing, and kinesiophobia. Sociodemographics, pain characteristics, diagnosis, lifestyle, health-related quality of life and treatment efficacy were compared among clusters. A prediction model was built utilizing a minimum set of questions to reliably assess cluster allocation. Among 5466 patients with chronic pain, three clusters emerged. Cluster 1 (n=750) was characterized by high psychological burden, low health-related quality of life, lower educational levels and employment rates, and more smoking. Cluster 2 (n=1795) showed low psychological burden, intermediate health-related quality of life, higher educational levels and employment rates, and more alcohol consumption. Cluster 3 (n=2909) showed intermediate features. Pain reduction following treatment was least in cluster 1 (28.6% after capsaicin patch, 18.2% after multidisciplinary treatment), compared to >50% for both treatments in clusters 2 and 3. A model incorporating 15 psychometric questions reliably predicted cluster allocation. **In conclusion,** our study identified distinct chronic pain patient clusters through 15 psychological questions, revealing one cluster with notably poorer response to conventional treatment. Our prediction model, integrated in a web-based tool, may help clinicians improve treatment by allowing patient-subgroup targeted therapy according to cluster allocation.
Perspective: Hierarchical clustering of chronic pain patients identified three subgroups with similar pain intensity and diagnoses but distinct psychosocial traits. One group with higher psychological burden showed poorer treatment outcomes. A web-based tool using this model could help clinicians tailor therapies by matching interventions to specific patient subgroups for improved outcomes.

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Introduction

Every day, health care providers face challenges treating chronic pain patients, as treatment effects are often disappointing. The "numbers needed to treat (NNT)" for commonly used analgesic drugs, e.g. anti-neuropathics, fall within the 3 to 10 range.[1] Recognizing that, depending on the drug, 3 to 10 patients must be treated for a 50% pain reduction in one patient, can be disheartening, as it entails treatment failure in the remaining patients. This is especially poignant as analgesic drugs prescribed for chronic pain can have serious side effects, such as opioid dependency and substance use disorder.[2] Hence, our approach to chronic pain treatment demands a transformation, and a potential solution involves deepening our understanding of the distinct characteristics found in clinical subgroups of patients experiencing chronic pain.[3,4] The identification of such subgroups could improve pain management by allowing treatment to be tailored to the needs and characteristics of each subgroup, ultimately reducing NNT's. Identification of such patient subgroups should include biopsychosocial components, as chronic pain is a complex multi-faceted problem with important biological (e.g., genetics), psychological (e.g., anxiety, depression, catastrophizing), and social (e.g., low educational attainment, poor social support) factors all determining the experience of chronic pain. Several studies have supported the hypothesis of chronic pain subgroups in specific populations, such as chronic low back pain,[5] temporomandibular disorder [6] and fibromyalgia,[7] whereas other studies have attempted to cluster patients in heterogenous chronic pain populations with a mix of painful conditions.[8–12] The available studies highly vary in their use of clustering variables, psychometric instruments and statistical methods. Clusters were based on unidimensional variables of pain-related characteristics such as pain location, or used a more multidimensional approach. Combining the main results of these studies, 2 to 4 reliable clusters emerge with psychiatric symptoms such as anxiety and depression, as well as the psychological construct of catastrophizing, proving most important for cluster allocation. A clear relation with the biomedical domain (including pain diagnosis) and the social domain (including lifestyle, educational level and employment) is still missing. Likewise, it remains unclear whether different subgroups respond differently to some analgesic therapies than other subgroups.

The current study aimed to identify different chronic pain subgroups using psychological variables and to compare subgroups on all three dimensions of the biopsychosocial model. Data were derived from validated questionnaires that were used to assess mental and social health status in a heterogenous patient population in a tertiary outpatient pain clinic. The derived subgroups were compared in terms of sociodemographic characteristics, lifestyle factors, perceived health related quality of life (HRQoL), pain diagnosis, and treatment response. A secondary aim was to alleviate the burden on patients currently tasked with completing multiple (extensive) pain questionnaires, by identifying those questions that are essential for cluster allocation, and suggesting a concise questionnaire for this purpose. Additionally, we aimed to test whether pain reduction following treatments was different between the clusters, which may help in designing patient-subgroup targeted therapy according to cluster allocation.

Methods

Study design

In this retrospective cross-sectional cohort study all chronic pain patients referred to the tertiary multidisciplinary outpatient pain clinic of the University Medical Center Utrecht (UMCU) between May 2018 and May 2021, and of the Erasmus Medical Center Rotterdam (EMC), The Netherlands, between January 2017 and March 2023, were included. The Medical Research Ethics Committees of the UMCU (MEC-21/358) and of the EMC (MEC-2023–0161) both approved this study and waived the requirement to obtain informed consent. Patients contributed indirectly to the design of this research by communicating their desire to reduce the burden of answering multiple lengthy questionnaires to the clinicians involved in the study. Consequently, the prediction model was designed with a minimal number of questions.

Data collection

Data were derived from questionnaires and standard entry boxes in the electronic health records that were collected as part of routine clinical care. Patients completed online questionnaires prior to their initial visit to the outpatient pain clinic. A combination of different patient-reported measures related to pain characteristics, psychological distress and health related quality of life (HRQoL) variables were included. These are described below.

Sociodemographic and pain measures

Sociodemographic data. Sociodemographic variables assessed were age (years), sex, Body Mass Index (BMI; kg/m^2), lifestyle behaviors (alcohol consumption, drug use, smoking), having children, employment status, educational level, marital status and major life events (presence or absence, open to patients' own definition).

Pain intensity, characteristics, duration and interference. Pain intensity was assessed using a 0 to 10 Numerical Rating Scale (NRS), with 0 equating to no pain and 10 to the worst imaginable pain, for the average, minimal and maximal pain intensity in the previous week.

We addressed *pain characteristics* in the UMCU using the first two questions of the Douleur Neuropathique en 4 (DN4) questionnaire comprising seven items (i.e., burning, painful cold, electric shock, pins and needles, tingling, numbness and pruritus) with a dichotomous yes-no scale. The total sum scores ranged from 0–7, with a cut-off point of ≥ 3 suggesting neuropathic pain.[13] The (Dutch) DN-4 has been validated in the general chronic pain population.[14] In the EMC, pain characteristics were assessed using the validated PainDetect, a 9-item self-report screening questionnaire.[15] It measures seven aspects of the quality of the pain experienced (i.e., burning, tingling, electric shocks, cold and heat hypersensitivity, numbness and pressure pain), the chronological pattern (time course), and whether or not the pain radiates. It is scored from 0 to 38, with total scores of less than 12 considered to represent nociceptive pain, 13–18 possible neuropathic pain, and scores $\geq$19 representing >90% likelihood of neuropathic pain.

For *pain duration*, patients indicated whether their pain persisted for more or less than one year.

Pain interference was assessed using the short form of Brief Pain Inventory (BPI) including seven items: general activity, mood, walking ability, normal work, relation with other people, sleep, and enjoyment of life. Each item was presented separately and was rated on a NRS scale from 0 to 10, with 0 indicating 'no interference of pain with daily functioning' and 10 'complete interference'.[16,17]

Pain diagnosis. Patients were diagnosed during their first visit to the outpatient pain clinic by their attending anesthesiologist-pain specialist. Pain diagnoses were assessed according to the International Classification of Diseases 10 registry (ICD-10).[18]

Treatment effect. Treatment effect was assessed using the *Global Perceived Effect (GPE)* questionnaire. The GPE asks the patient to rate, on a 7-point Likert scale, how much their condition has improved or deteriorated since the start of treatment.[19] In the UMCU cohort a subgroup of patients with peripheral neuropathic pain or scar pain received a high concentration capsaicin 8% skin patch. Treatment effect was measured 14 days after capsaicin treatment. In the EMC cohort, treatment effect was measured three months after treatment initiation at the tertiary pain clinic. The treatment at the EMC is multidisciplinary and

can include pain interventions such as nerve blocks and/or neuromodulation, drug treatment, physiotherapy, or psychological interventions or a combination of these treatments.

Psychological distress variables

Psychological distress was measured using three different questionnaires. The *Hospital Anxiety and Depression Scale (HADS)* self-assessment questionnaire assesses the level of anxiety and depression symptoms.[20,21] The *Pain Catastrophizing Scale (PCS)* assesses catastrophizing in three dimensions: magnification, rumination and helplessness.[22–24] The *Tampa Scale of Kinesiophobia (TSK)* questionnaire assesses fear of movement and injury.[25]

Health-related Quality of life

In the UMCU cohort, patients completed either the European Quality of Life instrument (EQ5D) or 12-item Short Form Health Survey (SF-12), because clinical practice changed during the study period, with a switch from the EQ5D to the SF-12. In the EMC cohort, the 36-item Short Form Health Survey (SF-36) was used. Details of the abovementioned questionnaires are reported in the Supplementary file to this methods section.

Statistical analyses

A statistical analysis plan was formalized before accessing the data for the primary outcome. No statistical power calculation was conducted prior to the study and all available data were included. Hierarchical clustering was performed on psychological variables using the individual questions of the HADS-A, HADS-D, PCS and TSK questionnaires. We chose these questionnaires as anxiety, depression and catastrophizing are closely linked to chronic pain, as they can exacerbate pain perception, increase emotional distress, and contribute to the persistence and intensity of pain symptoms,[26] and the HADS-A, HADS-D, PCS and TSK were used by both study centres. We decided to leave HRQoL out of the cluster analysis, as patients filled out either the EQ5D, the SF12, or the SF-36, which would lead to exclusion of a large number of patients. We also did not include the average pain intensity during the last week (NRS) and pain interference (BPI) data in the final model as 30% of the EMC dataset would be excluded. We did perform a sensitivity analysis including the NRS and BPI in the final model.

All patients with at least one missing value for one of the questions were excluded from this analysis. No imputation of missing data was performed as this could influence the clustering analysis.[27]

Hierarchical clustering was performed using the Gower's distance and the Ward's D2 clustering algorithm. Our approach was data driven (unsupervised), meaning that we did not assume a specific number of clusters before the analysis. Clusters were defined using a tree cut, and the number of clusters was defined using the elbow method based on the silhouette score. The derived clusters were compared for pain intensity, duration, characteristics and interference, pain diagnosis, sociodemographic variables, and HRQoL using one-way ANOVA for normally distributed continuous variables and Pearsons-Chi-square tests for categorical variables. Continuous normally distributed data were expressed as mean with standard deviation or 95% confidence intervals, categorical data as counts and percentages, and medians with interquartile range were chosen for NRS data as this data was not normally distributed. Statistical significance was set at $p \leq 0.05$. Subsequently, effect sizes of the observed significant differences were estimated using eta squared with <0.06 classified as small, 0.06 to 0.14 as medium and $\geq$ 0.14 as a larger effect size or using Cramér's V with 0.1 to 0.3 as a small, 0.3 to 0.5 as a medium, and $\geq$ 0.5 as a large effect size (47).

Four random forest models were trained on both the merged UMCU and EMC dataset. First a model was trained based on all questionnaire features. Using the Gini impurity index the top 10, 15 and 20 most important features were determined, and individual models were trained with those features. These 4 models were trained using 500 trees with out-of-bag permutations with a 3-times 10-fold cross-validation.

We analysed differences in treatment effect in subsets of patients. At the UMCU, we selected patients receiving the Capsaicin 8% patch for peripheral neuropathic or scar pain as they undergo standardized follow-up by our nurse practitioners, minimizing missing data. This makes it the most reliable treatment for comparison across clusters. To also add an evaluation on tertiary multidisciplinary pain management in general, we added the Erasmus treatment data as a second analysis. Differences in treatment effect were based on the results of the GPE and percentage of change in the NRS score between baseline and follow-up. Answers to the GPE were reduced to a dichotomous variable of "improved" (including little improvement, much improvement, and fully recovered) or "not improved" (including unchanged, little worse, much worse, and very bad) after treatment, because our dataset did not have sufficient power to analyze the efficacy across all seven outcome categories. Differences in treatment effects were analysed using a Pearsons-Chi-square test with improvement yes/no as outcome parameter, and a paired T-test for pain decrease (NRS) as outcome measure. Statistical analyses were performed using IBM SPSS Statistics version 26.0 to compare the clusters for pain intensity, duration, characteristics and interference, pain diagnosis, sociodemographic variables, and HRQoL). Hierarchical clustering and the training of the random forest models were performed using R version 4.2.2.

Results

Sample description

In total, 8133 patients were included in the study, of whom 2654 were referred to the UMCU and 5479 to the EMC. Of these, 1043 (UMCU; 39%) and 1624 (EMC; 30%) were excluded due to one or more missing values in the questionnaires used for cluster analysis, resulting in 1611 UMCU patients and 3855 EMC patients in the final analysis (Fig 1). No clinically relevant differences were observed when comparing the datasets of eligible patients with those used for analysis regarding age and sex (Table S1).

The patients in the UMCU cohort were slightly older than in the EMC cohort (mean age 54.5 years (SD=15.9) versus 49.9 (SD=15.6)). There

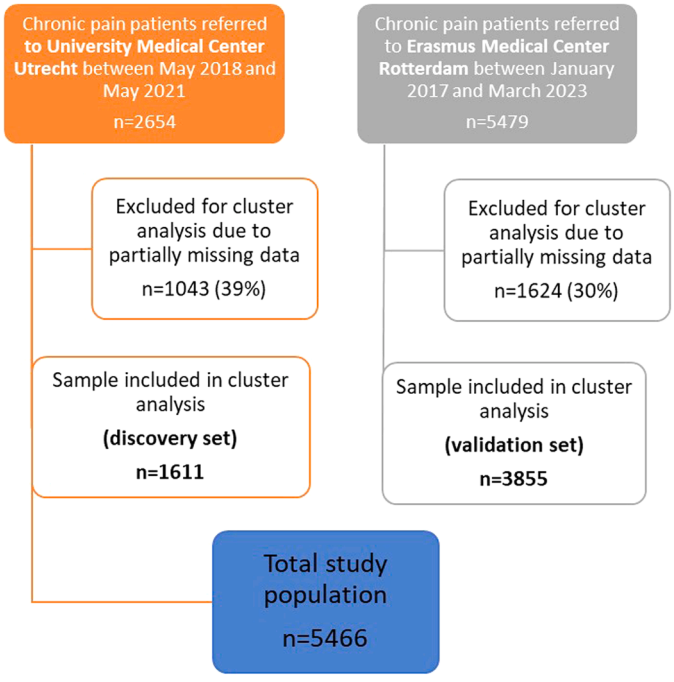

Fig. 1. Flowchart of study population.

were fewer females included in the UMCU population (53.9% females versus 64.2% in the EMC). The majority in both cohorts was married or cohabiting (UMCU 77.3% and EMC 75.0%) and had children (UMCU 71.5% and EMC 68.2%). A minority of patients was employed (UMCU 35.8% and EMC 37.1%) (Table 1).

Table 1
Sociodemographics, pain intensity, duration, character, interference and health-related quality of life in the study population (University Medical Center Utrecht and Erasmus Medical Center Rotterdam).

Variables	Total sample UMCU (n=1611)	Total sample EMC (n=3855)
n	1611	3855
Age in years (mean, SD)	54.5 (15.9)	49.9 (15.7)
Sex (% female)	829 (53.9)	2478 (64.2)
BMI in kg/m^2 (mean, SD)	26.7 (8.0)	24.2 (4.9)
Daily smoking (% yes)	269 (17.3)	638 (23.6)
Regular alcohol consumption (% >3 days per week yes/no)	273 (17.5)	NA
Drugs (% used once or more, yes/no)	102 (6.6)	NA
Highest educational level (%)		
Primary education	40 (2.9)	318 (8.3)
Secondary education	578 (41.8)	825 (21.4)
Vocational education	388 (27.9)	1727 (44.9)
University	87 (6.3)	897 (23.3)
Education not specified	291 (21.1)	80 (2.1)
Employment status (%)		
Student	38 (2.5)	114 (4.2)
Retired	397 (25.7)	468 (17.3)
Homemaker	49 (3.2)	256 (9.5)
Volunteer	34 (2.2)	NA
Unemployed	462 (29.9)	811 (30.0)
Employed	552 (35.8)	1003 (37.1)
Other	11 (0.7)	50 (1.8)
Marital status (%)		
Single	353 (22.7)	956 (24.9)
Cohabitation/marriage	1200 (77.3)	2891 (75)
Children (% yes)	1114 (71.5)	1842 (68.2)
Life-changing events (% yes)	830 (54.2)	NA
Average pain (NRS; median with IQR)	7 (2)	8 (2)
Minimum Pain (NRS; median with IQR)	4 (3)	5 (4)
Maximum Pain (NRS; median with IQR)	9 (2)	9 (1)
Pain duration (%) ≥ 1 year	71.3	86.4
Neuropathy (DN4)		
Median	5 (3)	NA
Score >3 (%)	71.4	NA
Neuropathy (PD) >90% Certainty (%)	NA	39.9
Brief Pain Inventory (NRS; median with IQR)		
General Activity	7 (3)	7 (2)
Mood	6 (4)	7 (3)
Walking ability	7 (5)	7 (5)
Normal Work	7 (3)	8 (3)
Relations with other people	5 (5)	6 (5)
Sleep	7 (4)	7 (4)
Enjoyment of life	6 (5)	7 (5)
Health-Related Quality of Life (mean, SD)		
SF12 Physical	25.4 (9.0)	NA
SF12 Mental	42.8 (7.2)	NA
SF36 Physical	NA	31.9 (7.9)
SF36 Mental	NA	45.1 (9.5)
EQ5D-VAS (0–100)	42.8 (25.9)	NA
EQ5D Index	0.74 (0.2)	NA

Data expressed as mean (SD - standard deviation), median (IQR - interquartile range) or count (%). NRS data is expressed as median with interquartile range as the data is not normally distributed.
BMI: Body Mass Index; DN4: Douleur Neuropathique en 4; EMC: Erasmus Medical Center Rotterdam; EQ5D: European Quality of Life instrument 5; EQ5DVAS: European Quality of Life instrument 5-Visual Analogue Scale; NRS: Numeric Rating Scale; PD: PainDetect; SF12: Short Form-12; SF36: Short Form-36; UMCU: University Medical Center Utrecht.

In the EMC cohort, more patients had experienced pain for more than 1 year (86.4% versus 71.3% in the UMCU cohort), with no difference in pain intensity between the cohorts (median NRS in the past week in UMCU cohort was 7 (IQR= 5–9) versus 8 (IQR= 6–10) in the EMC). We cannot meaningfully compare presence of neuropathic pain characteristics between both cohorts as two different questionnaires (DN4 and PainDetect) were used (Table 1).

In the UMCU cohort, the most common diagnoses were radicular syndrome (24.7%), mechanical spine related pain (11.6%), and mononeuropathy (8.1%) (Table 2). In the EMC, this was "other neuropathic pain" (17.5%), radicular syndrome (17.0%) and tendomyogenic pain (12.1%) (TableS2).

Hierarchical clustering revealed 3 clusters of patients

We first performed a hierarchical clustering on the UMCU dataset using the individual questions of the HADS-A, HADS-D, PCS and TSK questionnaires. We identified 3 distinct clusters of patients: Cluster 1 included 181 patients (11.2%), Cluster 2 comprised of 807 patients (50.1%), and Cluster 3 of 623 patients (38.7%) (Fig 2).

Cluster 1 was characterized by higher scores for anxiety (HADS-A mean 14.2; SD=3.7), depression (HADS-D mean 14.5 (SD=2.9)), catastrophizing (PCS mean 43.4; SD=5.7) and kinesiophobia or pain related fear (TSK mean 50.7; SD=8.0). Cluster 2 on the other hand was characterized by the lowest scores for each of these characteristics (HADS-A mean 4.1; SD=2.7, HADS-D mean 4.7; SD=3.0, PCS mean 16.2; SD=8.1 and TSK 35.1; SD=6.5), while Cluster 3 showed intermediate scores, at or just passing the cut-off scores for anxiety, depression, catastrophizing and kinesiophobia (HADS-A 8.8; SD=3.5, HADS-D 9.9; SD=3.6, PCS 29.0; SD=8.6 and TSK 43.2; SD=7.0).

Our second step was to perform a hierarchical clustering on the EMC dataset using the same questionnaires as a validation of our results with the UMCU dataset. We again identified 3 distinct clusters of patients with a comparable distribution: Cluster 1 included 1235 patients (32.0%), Cluster 2 1625 patients (42.2%), and Cluster 3 comprised of 995 patients (25.8%) (Fig 3). Again Cluster 1 was characterized by higher scores for anxiety, depression, catastrophizing and kinesiophobia or pain related fear (HADS-A mean 10.6; SD=4.4, HADS-D 11.7; SD=4.4, PCS 38.0; SD=7.8 and TSK 43.9; SD=7.2). Cluster 2 by the lowest scores for each of these characteristics (HADS-A mean 4.1; SD=2.7, HADS-D mean 4.4; SD=3.5, PCS mean 12.5; SD=8.1 and TSK 33.7; SD=6.0), while Cluster 3 showed intermediate scores again (HADS-A 6.4; SD=3.2, HADS-D 6.6; SD=3.6, PCS 23.3; SD=6.8 and TSK 41.4; SD=5.7), suggesting that there are indeed three distinct chronic pain patient subgroups, based on cluster-analysis on two different cohorts.

Table 2
Frequencies of the 10 most common diagnoses in each cluster for the UMCU cohort.

	Total	Cluster 1	Cluster 2	Cluster 3	p-value
Top 10 Diagnoses (%)					0.070
1. Radicular syndrome	24.7	17.1	26.5	24.6	
2. Mechanical spine related pain	11.6	11.0	10.5	13.2	
3. Mononeuropathy	8.1	8.8	8.8	7.1	
4. Joint pain	7.3	8.3	7.4	6.9	
5. Polyneuropathy	5.7	6.6	4.8	6.4	
6. Post-surgical pain	5.6	5.5	5.2	6.1	
7. Orofacial pain	4.4	3.9	4.3	4.7	
8. Abdominal pain	4.2	3.3	4.8	3.7	
9. Myofascial pain	4.2	5.0	4.5	3.7	
10. Widespread pain	2.4	6.1	2.0	1.8	

Data expressed as percentage per cluster. Significance levels computed by Pearson-Chi square.
There is no missing data.

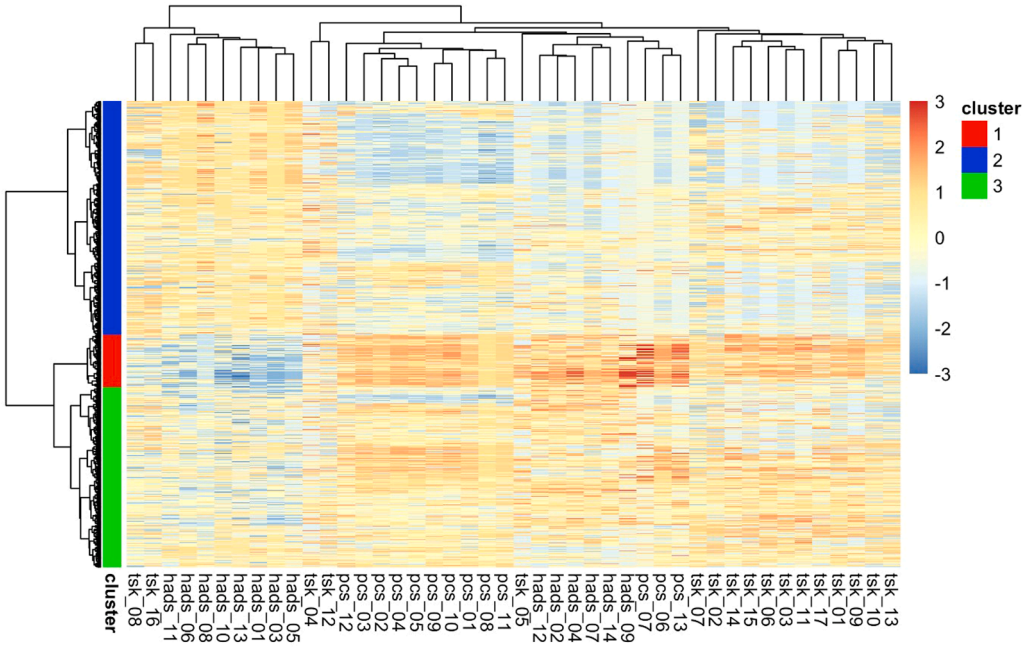

Fig. 2. Hierarchical clustering on UMCU cohort. Hierarchical clustering revealed three clusters: Cluster 1 (red), Cluster 2 (blue) and Cluster 3 (green). Columns represent the individual questions of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS), and Tampa Scale of Kinesiophobia (TSK). Each row represents one patient.

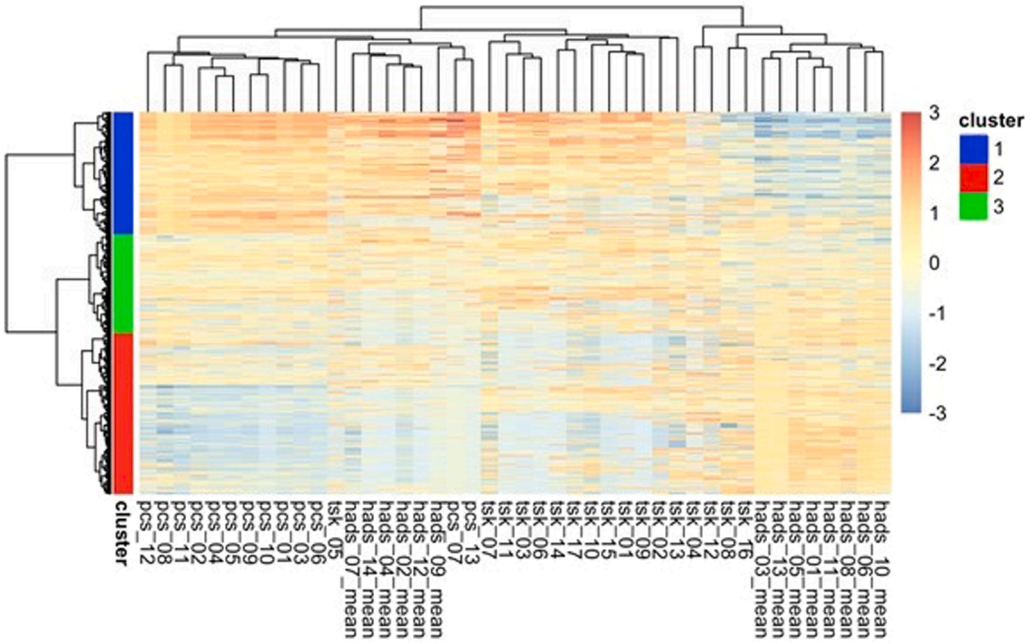

Fig. 3. Hierarchical clustering on the Erasmus MC cohort. Hierarchical clustering revealed three clusters: Cluster 1(blue), Cluster 2 (red) and Cluster 3 (green). Columns represent the individual questions of three questionnaires (Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS), and Tampa Scale of Kinesiophobia (TSK). Each row represents one patient.

Differences between the clusters in pain characteristics, sociodemographic characteristics and lifestyle behaviors, in the two cohorts

In the UMCU cohort, *pain* was most severe in cluster 1 with the highest intensity (median pain during the past week NRS 9; IQR= 8–10), longest duration (76.8% over one year) and highest prevalence of neuropath (83.6%). Cluster 2 showed lowest pain severity scores (NRS 7; IQR= 5–9, pain duration > 1 year in 67.8% of patients, 67.3% show signs of neuropathy) and Cluster 3 intermediate scores (NRS 8; IQR= 7–9, pain duration > 1 year in 74.1% of patients, 73.2% signs of neuropathy). Differences were significant between groups (Table 3).

In the EMC cohort, some different observations were made. Pain intensity and duration were comparable between clusters. Signs of neuropathic pain however were most often observed in Cluster 2 (50.8%), compared with 31.9% in cluster 1 and 39.5% in Cluster 3. All differences had a small effect size (TableS3).

In Cluster 1, widespread pain (UMCU cohort) and tendomyogenic pain (EMC cohort) were most prevalent, and radicular syndrome least

Table 3
Sociodemographics, pain intensity, duration, character, interference and health-related quality of life in the UMCU cohort and comparison among the clusters.

Variables	Total sample (n=1611)	Cluster 1 (n=181, 11.2%)	Cluster 2 (n=807, 50.1%)	Cluster 3 (n=623, 38.7%)	*p*-value	*Effect size*
Age in years (mean, SD)	54.5 (15.9)	53.7 (16.4)	54.7 (16.9)	54.6 (17.2)	0.776	
Sex (% female)	53.9	50.0	56.1	52.3	0.202	
BMI in kg/m^2 (mean, SD)	26.7 (8.0)	26.9 (4.4)	27.1 (10.2)	26.2 (5.1)	0.578	
Daily smoking (% yes)	17.3	26.0	11.8	21.8	<0.001	0.149
Regular alcohol consumption (% >3 days per week yes/no)	17.5	9.0	20.9	15.7	<0.001	0.103
Drugs (% used once or more, yes/no)	6.6	7.3	5.5	7.7	0.250	
Highest educational level (%)						
Primary education	2.9	13.5	0.9	2.2		
Secondary education	41.8	47.2	36.0	47.4		
Vocational education	27.9	24.5	29.7	26.8	<0.001	0.198
University	6.3	5.0	7.9	4.7		
Education not specified	21.1	9.8	25.5	18.9		
Employment status (%)						
Student	2.5	1.1	2.6	2.7		
Retired	25.7	25.3	26.9	24.3		
Homemaker	3.2	4.0	2.1	4.4		
Volunteer	2.2	2.9	1.9	2.4	<0.001	0.211
Unemployed	29.9	48.9	21.4	35.6		
Employed	35.8	14.9	44.7	30.2		
Other	0.7	2.9	0.4	0.5		
Marital status (%)						
Single	22.7	33.3	19.7	23.6	<0.001	0.101
Cohabitation/ marriage	77.3	66.6	80.3	76.4		
Children (% yes)	71.5	73.4	70.6	72.2	0.690	
Life-changing events (% yes)	54.2	50.9	58.3	49.9	0.006	0.006
Average pain (median NRS (IQR))	7 (2)	9 (1)	7 (2)	8 (1)	<0.001	0.275
Minimum Pain (median NRS (IQR))	4 (3)	6 (3)	4 (3)	5 (3)	<0.001	0.254
Maximum Pain (median NRS (IQR))	9 (2)	10 (1)	8 (1)	9 (2)	<0.001	0.243
Pain duration (%) ≥ 1 year	71.3%	76.8	67.8	74.1	0.015	0.079
Neuropathy (DN−4)						
Total score	5 (3)	5 (3)	3 (3)	4 (3)	<0.001	0.150
Score >3 (%)	71.4%	83.6	67.3	73.2		
Brief Pain Inventory (median NRS (IQR))						
General Activity	7 (3)	8 (2)	6 (3)	7 (2)	<0.001	0.288
Mood	6 (4)	8 (2)	5 (4)	7 (3)	**<0.001**	**0.376**
Walking ability	7 (5)	8 (2)	5 (6)	7 (3)	<0.001	0.232
Normal Work	7 (3)	9 (2)	7 (4)	8 (2)	<0.001	0.277
Relations with other people	5 (5)	8 (3)	3 (6)	6 (4)	**<0.001**	**0.321**
Sleep	7 (4)	8 (3)	6 (5)	7 (3)	<0.001	0.247
Enjoyment of life	6 (5)	8 (3)	5 (5)	7 (3)	**<0.001**	**0.365**
Health-Related Quality of life (mean, SD)						
SF12 Physical	25.4 (9.0)	20.6 (6.5)	27.9 (9.6)	23.3 (7.8	**<0.001**	**0.089**
SF12 Mental	42.8 (7.2)	39.2 (5.7)	44.1 (7.3)	42.0 (7.0)	<0.001	0.048
EQ5D-VAS (0−100)	42.3 (25.9)	29.5 (27.0)	49.0 (25.5)	39.0 (23.6)	**<0.001**	**0.070**
EQ5D Index	0.74 (0.2)	0.64 (0.1)	0.78 (0.1)	0.72 (0.1)	**<0.001**	**0.334**

Sociodemographic data expressed as mean (SD - standard deviation) or count (%). Questionnaire scores are expressed as median (IQR - interquartile range) or count (%). Statistics computed by one-Way ANOVA Test or Pearson Chi-Square test. Effect sizes for continuous data were estimated using eta squared with <0.06 as small, 0.06 to 0.14 as medium and ≥0.14 as a larger effect size. Effect sizes for categorical data are calculated with Cramer's V. Significance levels computed by Pearson Chi-Square test and effect sizes with Cramer's V indicating small 0.1 to 0.3, medium 0.3 to 0.5 and large >0.5 effect sizes. **Significant differences with medium to large effect size are in bold.**

Percentage of missing data: age 0.3%, sex 4.6%, BMI 76.0%, daily smoking 3.4%, regular alcohol 3.4%, drugs 3.4%, highest educational level 14.3%, employment status 4.3%, marital status 3.7%, children 3.4%, life-changing events 5.1%, pain NRS 0.2%, DN4 0,2%, BPI items 0.2%, TSK, HADS 0.3%, PCS 0.2%, SF12 43.8%, EQ5D 59.5%.

BMI: Body Mass Index; DN4: Douleur Neuropathique en 4; EQ5D: European Quality of Life instrument 5; EQ5D`-VAS: European Quality of Life instrument 5-Visual Analogue Scale; NRS: Numeric Rating Scale; SF12: Short Form-12; All p-values are corrected for multiple testing using the Bonferroni correction, adjusted p-values≤0.001 are considered significant.

prevalent (both cohorts). Complex regional pain syndrome (EMC cohort) was most prevalent in Cluster 2. Pain influenced HRQoL most in Cluster 1 in both cohorts (Table 3, TableS3). For all other diagnoses, there were no clinically relevant differences in prevalence among clusters (Table 2, TableS2). Overall, these data suggest that there is not a clear correlation between psychological characteristics and diagnosis.

Regarding *sociodemographic characteristics and lifestyle behaviors*, patients in Cluster 1 in both cohorts smoked tobacco more often and were more often single compared to cluster 2 and 3. Patients in Cluster 2 consumed more alcohol (in UMCU cohort; this was not recorded in the EMC cohort), had the highest educational levels, and the highest employment rates (Table 3, TableS3), indicating that there are differences in life style between clusters.

Treatment efficacy differences between clusters

Next, we tested whether medical treatment efficacy was different between the three clusters.

In a subgroup analysis of n=104 UMCU patients receiving a Capsaicin 8% patch for peripheral neuropathic pain or scar pain, 28.6% of those in Cluster 1 experienced improvement at 14 days follow up after treatment, compared to 58.9% and 55.9% in Cluster 2 and 3

respectively. In Cluster 1, although patients reported a small improvement on the GPE, maximum pain scores did not decrease significantly (NRS mean 8.9 (95%CI=8.4–9.5) to 8.6 (95%CI=8.0–9.3), p=0.391) at 14 days follow-up, while in Cluster 2 and 3 a significant reduction in maximum pain scores was observed (cluster 2 NRS mean 8.1 (95% CI=7.8–8.4) to 6.2 (95%CI=5.5–6.9), p<0.001; cluster 3 NRS mean 8.2 (95%CI=7.8–8.5) to 6.5 (95%CI=5.7–7.3), p<0.001) (Table 4).

In a subgroup analysis of n=497 (12.9%) EMC patients who received multidisciplinary pain treatment, treatment outcome was assessed three months after baseline. Improvement was reported in 18.2% of patients in Cluster 1, compared to 51.0% in Cluster 2, and 51.5% in Cluster 3 (Table 4), suggesting that cluster 1 may benefit form a different treatment approach.

Accurate prediction of cluster membership prediction using only 15 questions

Next, we aimed to build a prediction model of cluster membership as we believe those clusters are clinically relevant. As we found the same clusters in the 2 cohorts, we decided to merge the two datasets and use it to build the prediction model. As a sanity check, we first performed one more time a hierarchical clustering on the combined UMCU and EMC datasets (SupFig 1). When comparing the clusters obtained from the combined dataset (UMCU+EMC) with the clusters based on the individual datasets, we found that more than 75% of the patients were assigned to the same cluster.

We, then used a random forest approach to classify the patients of the combined cohorts based on their cluster membership (see methods). We reached an overall accuracy of 88%, with overall high sensitivity and specificity for each cluster (TableS4A).

To reduce patients' burden in having to answer multiple lengthy questionnaires, we next investigated whether we could reduce the number of questions and still obtain adequate accuracy, sensitivity and specificity for the prediction model. An advantage of a random forest model is that you know which variables are most important to accurately predict classes (using for instance the Gini index). Hence, we again built a prediction, but this time with only the 20 most important questions (SupFig2). This new model showed an accuracy of 87%, again with good sensitivity and specificity (TableS4B). Using the 15 most important questions resulted in an accuracy of 86% (TableS4C), while using the 10 most important questions yielded an accuracy of 84% (TableS4D). Overall, using the 15 most important questions seems to provide the best balance between number of questions and desired prediction accuracy. The prediction model has an approximate sensitivity for Cluster 1, 2 and 3 of 91%, 85% and 67%, and specificity of 89%, 94% and 99%, respectively. The top three most important questions for cluster allocation were 1. "When I'm in pain it's awful and I feel that it overwhelms me", 2. "I wonder whether something serious may happen", and 3. "I keep thinking about how badly I want the pain to stop".

In a post hoc sensitivity analysis, incorporating the average pain NRS and data from the BPI into the final model yielded consistent results (TableS5 and TableS6).

Developing a web-based tool to predict cluster membership

Finally, we developed a web-based tool with our prediction models in which the user can decide how many questions to use, enter manually the answers to those questions for a specific patient or upload a file with multiple patients' answers. As an output, the user will have for each patient, the probability to belong to each of the 3 clusters found in this study. This tool is freely available here: https://cti-compimmunocore.shinyapps.io/Pain_Clusters/.

Discussion

Treatment failure in chronic pain patients is common. Our aim was to identify subgroups of patients that are more or less likely to respond to certain interventions, so we can tailor subgroup-specific treatments to improve pain management. Based on the HADS, PCS and TSK questionnaires, we identified three chronic pain subgroups in a heterogeneous patient population (n=5454) in two tertiary outpatient settings using hierarchical clustering. Cluster 1 was characterized by high psychological burden, more tobacco smoking, lower educational levels, lower employment rates and more singles. Cluster 2 showed low psychological burden, more alcohol consumption, higher educational levels and higher employment rates. Cluster 3 showed intermediate features compared to the other clusters. Pain intensity and characteristics did not differ appreciably between the clusters in both cohorts. Regarding pain diagnosis, in Cluster 1 widespread pain (UMCU cohort) and tendomyogenic pain (EMC cohort) were most prevalent. Complex regional pain syndrome (EMC cohort) was most prevalent in cluster 2. For all other diagnoses, there were no clinically relevant differences in prevalence among clusters. Importantly, treatment success was comparable between Clusters 2 and 3, but was consistently and significantly lower in Cluster 1. We hypothesize that patients identified as belonging to cluster 1 may need a different treatment approach, with suggestions provided below.

Table 4
Treatment effect differs between clusters.

	Cluster 1	Cluster 2	Cluster 3	Pearson Chi Square p-value	Cramers V
UMCU – Capsaicin 8% patch	*N=14*	*N=56*	*N=34*		
GPE improved (number of patients (%))	4 (28.6)	33 (58.9)	19 (55.9)	Cluster 1 vs 2 p=0.119 Cluster 1 vs 3 p=0.267 Cluster 2 vs 3 p=0.992	
Max NRS before treatment (mean with 95%CI)	8.9 (8.4−9.5)	8.1 (7.8−8.4)	8.2 (7.8−8.5)	NA	
Max NRS after treatment (mean with 95%CI)	8.6 (8.0−9.3)	6.2 (5.5−6.9)	6.5 (5.7−7.3)	NA	
Paired t-test	*0.391*	*<0.001*	*<0.001*		
EMC-multidisciplinairy pain treatment	*N=11*	*N=257*	*N=229*		
GPE improved (number of patients (%))	2 (18.2%)	131 (51.0%)	118 (51.5%)	Cluster 1 vs 2 p=0.033 Cluster 1 vs 3 p=0.031 Cluster 2 vs 3 p=0.903	0.130 0.139

Treatment effect (global perceived effect and pain numeric rating scale) were assessed two weeks after application of a capsaicin 8% patch in patients with peripheral neuropathic pain or scar pain in a subgroup of patient in the UMCU cohort. Treatment effect (global perceived effect) was assessed three months after baseline after a multidisciplinary treatment in the EMC cohort. All available data was used.
The global perceived effect was categorized to "improved" of "not improved (including no change)". Data expressed as count (%). Significance levels computed by Pearson Chi-Square test and effect sizes with Cramer's V indicating small 0.1 to 0.3, medium 0.3 to 0.5 and large >0.5 effect sizes.
The pain numeric rating scale was calculated as mean and baseline and follow up NRS scores were calculated within clusters using a paired-sample t-test. P-values <0.05 were regarded as significant.

When comparing our results with existing literature on cluster analyses in chronic pain populations, most studies also note differences observed in the psychological domain. Some find 'extreme' groups akin to our Clusters 1 and 2, and an intermediate group like our Cluster 3.[5,7–12,28] The number of clusters varies between studies (2 to 9), likely due to differing populations or input variables. Our identification of three clusters in a heterogeneous chronic pain population aligns with two other studies.[12,28] Gerdle identified groups based on pain intensity, emotional distress, acceptance, and life impacts.[12] Gilam identified groups based on physical, mental, and social domains, with graded severity, mirroring our clusters.[28] Anxiety and depression, key in subgroup assignment in both studies, were also prominent variables in our study. Some studies added pain diagnoses; Bäckryd et al. [10] identified four subgroups with small differences in diagnoses distribution. Reviewing these studies and our cohorts, we assert that identifying three subgroups with graded psychological severity is a robust finding.

Psychological symptoms in chronic pain are linked to social factors like education, employment, lifestyle, and marital status. Unemployment, lowering socioeconomic status, often induces psychological stress.[29,30] Lower education levels and socioeconomic status correlate with higher pain prevalence and poorer health.[31–33] Possible explanations include increased exposure to risk factors, physically demanding jobs, unhealthy lifestyles, limited healthcare access, and higher stress exposure with poorer coping skills.[34] Health literacy may also contribute to this link.[35] In a study including 131 chronic pain patients, 54% had inadequate health literacy associated with lower education and income.[32] Our study found that Cluster 1, in contrast to Cluster 2, is associated with lower education and less university education and paid employment. Marital status also differed, with more singles in Cluster 1. Social support by romantic partners is suggested to have an analgesic effect, and the absence of such support in Cluster 1 may influence pain experiences.[33] Furthermore, both psychological symptoms and high severity of pain can lead to a decreased HRQoL.[36] It is therefore not surprising that the identified groups showed such a pattern and that two groups (Cluster 1 and Cluster 2) emerged with highly contrasting characteristics.

In the current study the prevalence of most pain diagnoses did not differ between the three clusters, and the difference in pain intensity and characteristics between clusters were small and only significant in one of our two cohorts. This suggests that the actual initial inciting stimulus or painful condition may be of lesser importance to the chronic pain experience (duration, impact and severity) than psychosocial factors are. While the psychosocial factors may not be exclusive or specific for chronic pain, pain treatment outcomes were significantly different between cluster 1 and the other two clusters. This suggests that patients from cluster 1 present with a unique set of psychosocial factors that may need a different treatment approach. Possible changes in pain management could include pain education tailored to the educational level of the patient to improve understanding of their disease, lifestyle coaching including cessation of smoking (associated with higher pain intensity, pain interference and pain-related fear [37]), and support by social workers finding a job and improving socioeconomic status reducing stress that is associated with worse pain. Naturally, patients with signs of a clinically significant anxiety or depressive disorder should be referred for psychiatric care, but we want to emphasize that this alone might not be enough, as the multidisciplinary treatment offered at the EMC (and also UMCU) included psychological and/or psychiatric referral when indicated.

There were three diagnoses: widespread pain, tendomyogenic pain and CRPS, which were not equally distributed across the clusters. Tendomyogenic pain and widespread pain are known to be associated with depression,[26] which may explain the higher prevalence in Cluster 1. CRPS is more often diagnosed in women which provides an explanation for the sex difference observed between both cohorts. In Cluster 2, CRPS was overrepresented, for which no clear underlying cause could be identified. The differences in the overall diagnosis distribution between the two centres seem mainly related to differences in research focus and healthcare expertise; the EMC is an expertise centre for CRPS, explaining the larger number of CRPS patients in their cohort.

This study has several strengths, including a large heterogenous chronic pain sample included at two multidisciplinary tertiary pain centres, with variables representing the different potential drivers of chronic pain according to the biopsychosocial model. However, this study also has several limitations that must be considered. First, approximately one third of patients had to be excluded from the hierarchical cluster analysis due to one or more missing values in the questionnaires. This large proportion of missing data might have biased the results, when patients not willing or not able to fill out all the questions are overrepresented in the excluded group. This especially holds true for the follow-up data in which we assessed the treatment efficacy between clusters. Second, the present results are based on a group of patients referred to a tertiary academic pain clinic, which tend to represent the most complex cases. Therefore, our findings may not generalize to other chronic pain populations and should be verified across different chronic pain patients and in different clinical settings. Third, race and ethnicity data were not available, impacting generalizability. Fourth, due to the cross-sectional design of this study, causality cannot be determined. Fifth, we performed the cluster analysis using only psychological variables, excluding pain and social characteristics, as these questionnaires were not consistently used across the two outpatient pain clinics. While other studies incorporated disease specific, pain and social variables,[10,38,39] we focused on psychological variables to ensure comparable results and prioritized validating our clusters with a second dataset. Lastly, the results are based on self-reported outcomes and could be biased by social desirability. People with higher educational levels may be more successful in manipulating their answers to questionnaires (such as the HADS, PCS and TCK) to reduce their psychological burden result and prevent a possible referral to the psychiatrist or psychologist when the patient is not motivated or open to such intervention.

Regarding clinical implications, the present study underlines the importance of acknowledging that the chronic pain population is not a homogenous group and indicates that therapeutic interventions should be adjusted to individual patient characteristics rather than only to pain diagnoses. Subgroup assignment using psychological variables can potentially help support clinical decision making by clinicians: Knowledge of subgroup patterns helps determine the most effective treatment option for the individual patient. It seems particularly important to identify patients that belong to Cluster 1, as patients with this subset of characteristics are likely at risk of high-impact chronic pain, associated with most suffering, unfavourable health outcomes, increased medical costs and opioid use.[40,41] With our prediction model we can reliably predict Cluster 1 allocation with an optimal number of questions of 15 with a sensitivity of 91.3% and a specificity of 79.9%. In future trials, the clinical relevance and treatment responses of subgroup-specific pain management approaches must be further evaluated. Using a brief questionnaire with only 15 questions could enhance response rates, contributing to the success of a trial.

In conclusion, using hierarchical clustering analysis on two independent cohorts, we identified three chronic pain subgroups with different psychological and sociodemographic characteristics based on patient-reported measures. Remarkably, these groups were largely unrelated to specific pain diagnoses. This knowledge can be potentially useful for tailoring subgroup-specific treatment plans to improve chronic pain management for individual patients. Using our prediction model, integrated in a web-based tool) including limited amount of questions only (10, 15 or 20), we can reliably predict cluster allocation, especially cluster 1, identifying patients who need a biopsychosocial approach with tailored pain education.

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Conflict of Interest

None of the authors has a conflict of interest to declare

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Author Contributions

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2025.104792.

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