Journal of Pain Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Using a Two-Steps Clustering and PCA Analysis for Stratified Chronic Non-Cancer Pain Care: A Retrospective Cross-Sectional Study

Ana M Peiró[1,2], Jordi Barrachina[1], Mónica Escorial[1], Isidro Aguado[1], César Margarit[1,3], Anna Grimby-Ekman[4]

[1]Neuropharmacology Applied to Pain (NED), Clinical Pharmacology Unit, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, 03010, Spain; [2]Institute of Bioengineering, University Miguel Hernández, Elche, 03202, Spain; [3]Pain Unit, Alicante Department of Health -General Hospital, Alicante, 03010, Spain; [4]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence: Ana M Peiró, Alicante Institute for Health and Biomedical Research (ISABIAL), Hospital General Universitario Doctor Balmis, c/ Pintor Baeza, 12, Alicante, 03010, Spain, Email apeiro@umh.es

Purpose: Given the number of people who suffer from chronic pain and the impact on healthcare resources, it is imperative that the people with pain receive an appropriate matched treatment due and stratified care. The aim of this study was to characterize chronic non-cancer pain (CNCP) patients' states, through an unsupervised cluster analysis, to implement clinical recommendations in pain care.

Patients and Methods: Real-world ambulatory CNCP cohort of patients (n = 418) completed a multidimensional patient-reported registry, as part of a routine initial evaluation, in a multidisciplinary academic pain unit. A clustering analysis was performed according to: 1) pain intensity and relief; 2) quality of life; 3) number of adverse events; and 4) emergency department visits. A retrospective study was developed (n = 120) following the stratified analysis.

Results: From a principal component analysis, cut-off points were defined to discriminate between the six clusters and three groups of different pain intervention requirements. Those patients showed a significantly different monitoring and basal clinical status. Being older than 65 years old, retired or on medical leave, under opioids and anxiolytic prescription, had a severe impact on daily quality of life without any sex-difference.

Conclusion: These clusters based on real-world clinical information might be useful for screening even more where the access to physical exploration is limited. Follow-up analyses will support the replicability of this stratified care.

Keywords: global pain status, chronic non-cancer pain, clustering analysis, quality of life, stratified care

Introduction

The underlying challenge of an optimal chronic non-cancer pain (CNCP) management is to choose the right health care for patients' needs that can enable a better quality of life.[1] In Europe there are approximately 740 million people, most of whom experience an episode of severe pain at some point in their life.[2] For approximately 20%, that pain persists for longer than three months and will be chronic pain. In fact, over time, individuals may become more vulnerable to stressors, thereby increasing the likelihood of experiencing pain that can also worsen the financial situation, adding to daily financial worries. This reinforces the importance of the topic.[3,4] In many cases CNCP is well managed or resolved in primary care treated using simple modalities as the patient can deal with their own pain with continued support.[5] In other cases of a painful severe condition, pain management needs to be escalated, with more specialist pain services becoming involved[6] and more complex case-management programs.[7–9]

Risk-based stratified care would involve targeting pain management as opioid prescription, according to patients' risk of persistent pain, for being more efficiently avoiding ie unnecessary interventions and cost.[10] Thus, targeting treatment to subgroups of patients could be a method to fast-track appropriate treatment reducing harm.[11–13] This stratified pain

Received: 28 August 2024
Accepted: 9 December 2024
Published: 11 February 2025

care needs to be timely as intensive pain accelerates over time through well-recognized pain outcomes.[14,15] The goal is to reduce unnecessary overtreatment in patients who have a good prognosis yet increases the likelihood of appropriate healthcare for those who are at risk of disabling pain.[16]

The present study has sought to understand how pain management outcomes are clustered together to define simple algorithms for pain management recommendations.[17,18] Knowing the profiles of people who suffer from pain could make it possible to detect associated risk, alert clinicians that may need further diagnostic evaluation or be derived to a specialist multidisciplinary pain management team.[19,20] We assumed that patients would need a most intensive clinical intervention, due to clinical data clusters, which could be explained through cut-off points. We thus aimed to characterize CNCP patients' states as risk groups linked to specific pain stratified care through an unsupervised cluster analysis that enabled us to stratify a data set without any previously defined hypothesis. Being pain the primary reason for referral to secondary care, this new tool could prioritize direct referral to specialized pain services.

Material and Methods

Patients and Ethics

A cross-sectional study was conducted from April to May 2024 in CNCP outpatients with long-term opioid prescription (≥6 months) in their regular visits to the Pain Unit (Alicante-Dr. Balmis General Hospital, Alicante, Spain) who had participated in previous studies from 2014 to 2017. All patients included were ≥18 years old with CNCP (moderate or severe pain lasting for six or more months) under long-term opioids (≥6 months). Here, we excluded patients who had difficulty communicating, vision or hearing problems, patients with chronic cancer pain and those with cognitive disorders.[21] Moreover, this study did not incorporate chronic pain conditions of unknown pathophysiology, such as fibromyalgia or neuropathic pain conditions (painful polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, and post-stroke pain).

Afterwards, a retrospective study was done due cluster stratification for random 20 patients from each of the three clusters, at the time of inclusion at the study (basal information) and the next Pain Unit visit (3-months later, final information). The study falls under the umbrella of a master protocol approved by the Research Ethics Committee of the Alicante-General Hospital (PI2019/108, 190,715), after being classified by Spanish Agency for Medicines and Health Products, which complies with the applicable STROBE guidelines, with the exemption of informed consent. This manuscript adheres to standardized questionnaire validation methods.

Measures and Outcomes

Socio-demographic and clinical information were registered from the original study database.[22] Employment status (active, retired, work disability, unemployed or homemaker) and monthly incomes (low income – less than €500, middle income – between €500–1000 and upper income – more than €1000) were collected.

Clinical variables as diagnosis, pain intensity/relief and quality of life determined using the validated 100 mm Visual Analogue Scale (VAS, 0 "no pain/relief" to 100 "worst possible pain/maximum relief") and Likert Scale with 5 categories for pain relief and intensity (4 = extremely intense, 3 = intense, 2 = moderate, 1 = mild, 0 = none). Health-related quality of life assessed by EQ-5D-3L due to self-reported health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, that allows us to obtain the utility score (0–1). EQ-VAS for the measurement of current health ranging from 0 (worst imaginable health) to 100 (best imaginable health).[23] All of them are validated and integrated in the Global Pain Status questionnaire (GPSq), a transversal instrument to determine the multidimensional pain clinical situation, developed in 2016 by Barrachina et al[15] in our Pain Unit (PU) environment. The questionnaire integrated previous one cited being easily to fullfight and interpreted by clinicians or nursery team.

Most frequent opioid adverse events (AEs) were listed including open fields: xerostomia, constipation, dizziness, dry skin, headache, somnolence, insomnia, weight change, loss of appetite, depression, nervousness, pruritus, nausea, edema, vomiting, erectile dysfunction, loss of libido and erythema.[24] A field was also left open in the list for free-text additions. AEs were defined as mild (0 to 1 adverse event), moderate (2 to 5 adverse events), and severe (6 or more adverse events). Hospital use as the percentage of Emergency Department (ED) visits, hospitalizations, or any drug changes due to pain or

other causes were registered when patients were included in the last month. Prescription changes included: 1) Change in any drug-dosage, 2) Product or generic brand switch, 3) Stopping medication or non-adherence, and 4) Starting a new medication.[25]

Drug Prescription

Simple analgesics (ie, paracetamol and metamizole), non-steroidal anti-inflammatory drugs (NSAIDs), opioids use (ie, tramadol, codeine, fentanyl, oxycodone, tapentadol, buprenorphine, morphine, hydromorphone and methadone), along with immediate release opioids prescription were registered. Using different opioids' combinations, oral morphine equivalent daily dose (MEDD) was estimated using available references.[26,27] The prescription of antidepressants (ie, amitriptyline, fluoxetine, escitalopram, and duloxetine), benzodiazepines and neuromodulators (pregabalin and gabapentin) were also collected.

Clinical Differences Between Clusters

To ensure the clinicals differences among patients from different clusters, we conducted an analysis to compare clinical variables including pain intensity, pain relief and quality of life, along with other variables such as opioid rotation, analgesic titration, opioid withdrawal or reduction, application of analgesic techniques, intensive monitoring, follow-up by the PU, follow-up by primary care or clinical session consultation. To accomplish this, we randomly selected 40 patients from each cluster for the respective analysis to register 3-months later information due to the clinical recommendations from cluster 0–2.

Statistical Methods

Patients' demographic information and disease characteristics were presented with descriptive statistics (mean, median with the interquartile range (IQR), frequency, and standard deviation). Convenience sampling was considered based on our regular clinical routine at the Pain Unit. Quantitative parametric data are presented as mean (standard deviation (SD)). Categorical data are expressed as percentages (%). The sample size of the purposive sample was 418 people (292 females, 125 males). Those sample sizes fit in with the CNCP global prevalence of 24% for women and 10% for men[28] and the Alicante population.[22,29]

Five items from the GPS questionnaire were used in the analysis. The Likert scales of pain intensity and pain relief were chosen instead of the corresponding VAS scales, as the VAS scales have non-linear properties.[15,19,25,30] The variables in GPS were recorded into standardized categories according to Likert pain intensity (range as 0 [0–1], 1 [2–3] and 2 [4 scores]), Likert pain relief (0 [4],1 [3–2] and 2 [0–1 scores]), VAS QoL (0 [>70],1[40–70] and 2 [<40 mm]). In this way, negative extreme patients (n = 18) would be as Likert Pain intensity as 4 score, Likert Pain Relief 0–1, VAS QoL <40 mm, ED Pain + Hosp Pain = both YES, number of AEs more than 5, Medication change = YES. In contrast, positive extreme patients would be as Likert Pain intensity as 0–1 score, Likert Pain Relief 4, and VAS QoL >70 mm, ED Pain + Hosp Pain = both no, number of AEs 0–1, Medication change = NO. The analyses were carried out separately due to sex, age, incomes and working status, with the intention of identifying possible differences between these variables.

Two-step cluster analysis in IBM SPSS Statistics (Version 28.0.1.0)[31,32] was used on the GPS instrument, to find a clinically based grouping of patients. The two-step cluster analysis first separates data into groups, and in the second step a probabilistic approach is used to choose an optimal subgroup model. Hence, the number of clusters was determined by Bayesian Information Criterion (BIC), a statistical measure of fit due the results and clinical coherence. Before the cluster analysis, the variables were transformed to a common standardized scale of 0, 1 and 2, with the lowest value meaning a positive outcome (low pain intensity, high pain relief, etc.) and the highest meaning a negative outcome. This transformation was based on the clinical experience and use of the GPS (Supplementary Table 1S). A descriptive analysis of the variables included (extreme definition, from the PSG) is shown in Supplementary Table 2S.

A principal component analysis (PCA) was performed on the 5 GPS items, and the first principal component dimension was seen as a one-dimensional scale of the level pain burden. This scale was then divided into groups, defined by its percentiles in each of the clustering groups and compared to the clustering results. A p-value < 0.05 was

considered statistically significant. For descriptive analysis R 4.0.3 and Graph Pad Prism 9 was used. Clustering analysis and logistic regression were carried out by using IBM SPSS Statistics (Version 28.0.1.0).

Results

A total of 924 patients were included from 1452 potential CNCP, long-term opioids treated, pre-screened candidates. However, 29 because they were not identifiable, 443 duplicates, 56 without opioid criteria (long-term > 6 months). The final sample was of 418 CNCP patients for cross-sectional study. All patients were Spanish and used the Spanish language.

Study Population

The mean age was 65–66 years old and nearly half the sample were retired (incomes between 500–1000 euros/month) with 11–12% of previous substance use disorder (SUD), mostly tobacco. For both sexes, lower back pain was the most common CNCP (80%), and the mean time under opioid treatment was 3 years. The baseline characteristics were quite similar in the total sample (n = 924) and sample included (n = 418), as shown in Tables 1 and 2.

Mean VAS pain intensity was moderate (59 ± 28 mm) whilst 50–53% of the sample labeled as severe-extremely severe on the Likert pain intensity scale. Similarly, VAS pain relief was mild (35 ± 30 mm) but labeled as none-mild by 50% of the population in Likert scale. We did not detect any significant difference for most of the variables, except that the percentage of participants with "extreme severe pain intensity" was slightly lower in the validation cohort than in the discovery cohort. VAS quality of life was moderate (44 ± 24 mm) with a utility due health status of 0.481–0.514. Due to hospital resources use, the higher issue was medication changes (29–34%). Emergency room visits rose 18–21% globally and hospitalization was required in 6–7% of the sample, due to pain.

Table 1 Socio-Demographic Analysis of the Population

Socio-Demographic	Total (n=924)	Algorithm Sample (n=418)	P-Value
Sex (% female, n=924, n=418)	65	70	0.118
Age (years old) (median (IQR) n=661, n=314)	65 (53–74)	66 (57–75)	0.195
Employment status (%, n=343, n=220)			
Active	18	19	0.826
Retired	54	56	0.665
Work disability	14	14	1.000
Unemployed	10	7	0.362
Homemaker	4	4	1.000
Incomes (%, n= 45, n=26)			
Less than €500	22	23	1.000
Between €500 to 1000	62	65	1.000
More than €1000	16	12	0.736
Previous substance use disorder (%, n=669, n=314)	12	11	0.753
Tobacco	12	11	0.915
Alcohol	0.5	0.3	1.000
Illicit substances	0.3	0	1.000

Table 2 Clinical Analysis of the Population

Clinical Data (%)	Total (n=924)	Algorithm Sample (n=418)	p-Value
Pain intensity (VAS, 0–100 mm, n=832, n=418)	59 ± 28	59 ± 28	0.642
Likert pain intensity (%, n=758, n=418)			
None	7	6	**0.036**
Mild	11	14	
Moderate	29	30	
Severe	34	37	
Extremely severe	**19***	13	
Pain relief (VAS, 0–100 mm, n=775, n=418)	35 ± 30	35 ± 29	0.893
Likert pain relief (%, n=568, n=418)			
None	29	32	0.357
Mild	21	18	
Moderate	29	32	
Severe	16	13	
Extremely severe	5	5	
Quality of life (VAS, 0–100 mm, n=806, n=418)	44 ± 24	45 ± 21	0.417
Quality of life (Health Status, 0–1 score) (median (IQR), n=146, n=113)	0.481 (0.113–0.710)	0.514 (0.080–0.715)	0.553
Health Resources Use data (%, n=756, n=418)			
Emergency room visits	27	31	0.906
Hospitalisation	13	16	
Medication changes	34	42	
Health Resources Use data due to Pain (%, n=731, n=418)			
Emergency room visits	17	19	0.042
Hospitalisation	6	7	
Medication changes	29	34	
Health Resources Use data due to Other Causes (%, n=570, n=312)			
Emergency room visits	18	21	0.698
Hospitalisation	10	14	
Medication changes	16	21	

Main Chronic Non-Cancer Pain Groups With Clustering

Characteristics related to CNCP were analyzed to identify groups of subjects. The two-step clustering of 5 items gave a solution with 6 clusters with a fair cluster quality, silhouette measure of cohesion and separation≈0.30. The majority of the parameters were significantly different between the states. All variables were important in clustering and ranking from most important to least important, see Figure 1. The most positive cluster was characterized by patients with none

https://doi.org/10.2147/JPR.S490442

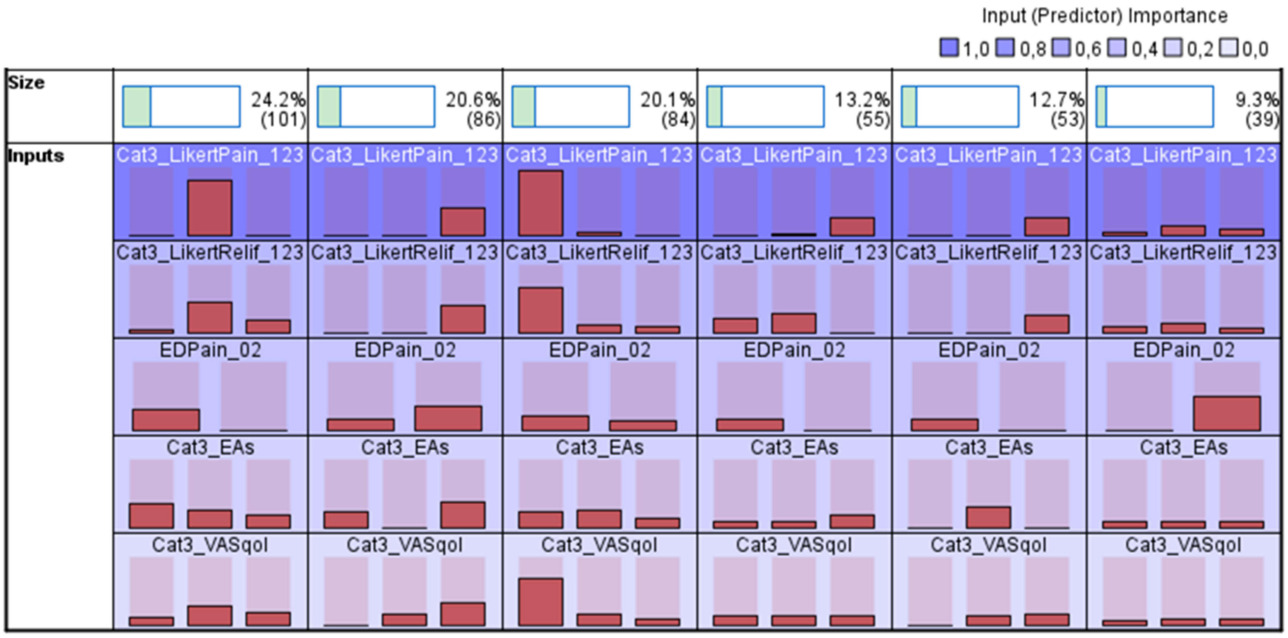


Figure 1 Distribution for each single question (GPS) in each cluster. Importance of the single questions, in the questionnaire GPS, to the two-step clustering solution (scale of importance featured in the upper right): Cat3_LikertPain_123=pain intensity, Cat3_LikertRelif_123=pain relief, EDPain_02= Emergency department visits due to pain, Cat3_EAs= frequent opioid adverse events and Cat3_VASqol=quality of life.

or mild pain intensity, severely or extremely relieved and none or one adverse event. The most extreme negative cluster was characterized by patients with severe or extreme pain intensity, not relieved or mildly relieved, and having >6 AEs. The ratio of the smallest to largest cluster size was acceptable at 2.40. Hence, the observations were split into 6 clusters with a size range from 9% to 24% of the total number of 418 patients.

A clinical guidance for intervention was connected to the 6 clusters classified broadly into three groups of pain management: Primary/Pain Unit standard or intensive care. The name of the 3 groups of people with CNCP found were based on the care level requirements by this health condition as follows: 'group 0-people with a low risk' (cluster 0, GP care), 'group 1-people with a medium risk' (original clusters 1–3, Pain Unit standard care) and 'group 2-people with a high risk' (original clusters 4–5, Pain Unit intensive care). The results show that 100% of the cases were correctly classified. This supports the results obtained in the previous cluster analysis.

Compared to the patients in Group 1 ("Low risk") that could be followed in primary care, those in Group 1 ("medium risk") were healthier in terms of every cluster-building variable, but seemed to be more affected than Group 0. They had a higher pain intensity, and lower pain relief but with similar impact on quality of life and tolerance. In order to ease these symptoms and to improve patient' physical strength and general well-being, a therapy focus on regular PU visits would be necessary for this group due to optimized therapy through analgesic titration or add another analgesic or neuromodulator co-prescription, always evaluating other options as analgesic techniques. Patients for Group 2 ("High risk") seemed to suffer more from their CNCP than those in previous clusters, especially in terms of less pain relief.

In the retrospective analysis (n = 120 patients) all 3 clusters were equally treated except for the higher intensive monitoring that was done for cluster 1 (37%) versus 20–24% of the rest clusters ($p < 0.05$). Clinical values shown in Figure 2 suggested a significantly higher pain intensity, lower pain relief and quality of life ($p < 0.05$) in cluster 2 at basal, with the same tendency at final visit (3-months later).

Factors Associated With CNCP Patients' Risk: Cut-off Points

When identifying factors associated with pain risk groups in the analysis, the first stages suggested the elimination of some of the variables. In Table 3 the clinical tool of the GPSq is presented. This includes the calculation of the principal component value and the GPS cut-off group, for a patient, based on the answers to the clinical questions (the 5 items).

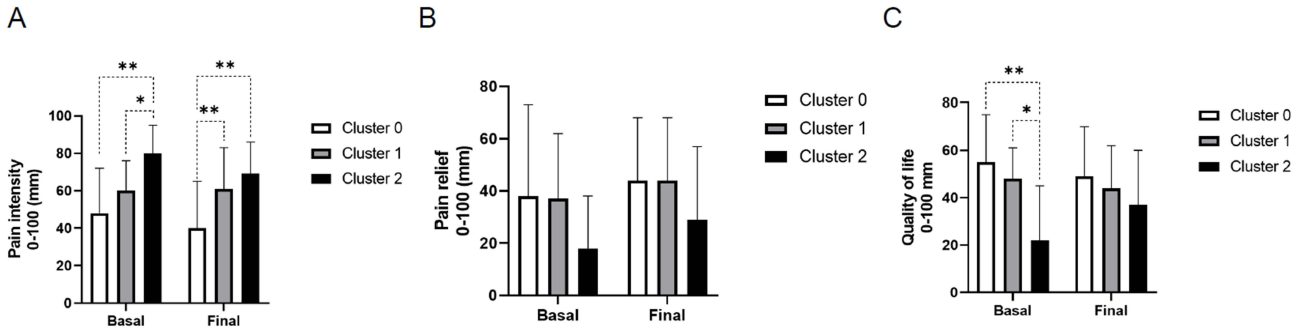


Figure 2 Showing the pain intensity (**A**), relief (**B**) and quality of life status (**C**) in the retrospective analysis of the clusters for future clinical guidance for intervention, based on clinical experience. * for p<0.05 and ** for p<0.001.

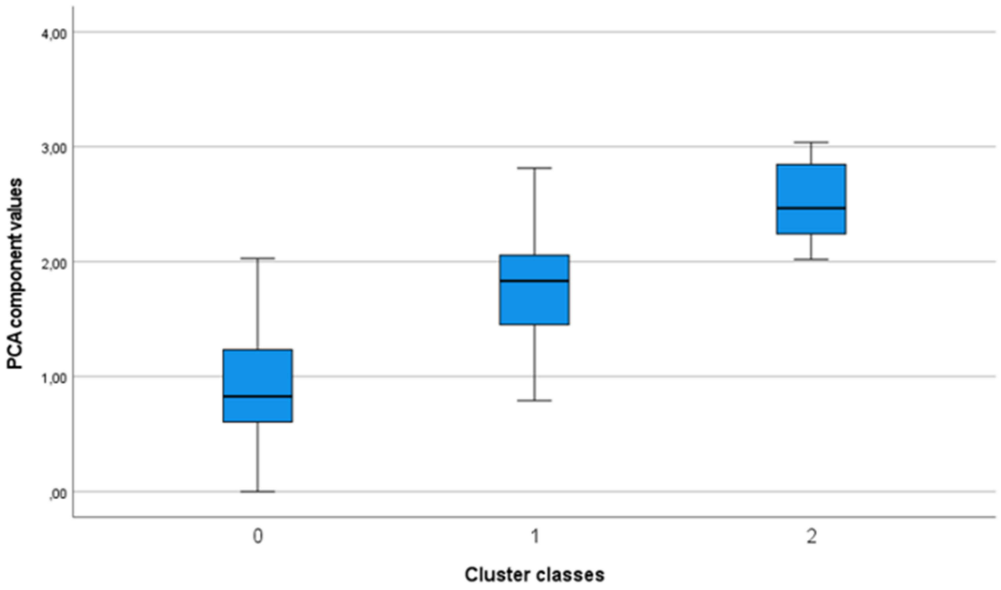
Thus, a principal component analysis was performed on the 5 selected GPSq outcomes (Likert pain intensity, relief, VAS quality of life, number AEs and ED visits), projecting them into one dimension, the first component. This PCA component explained 37% of the variation in the 5 items, and the loadings (Pearson correlations between each item and

Table 3 Calculating the Principal Component Value for a Patient, Based on the Clinical Questions (the 5 Items), and to Establish the GPS Cut-off Group for the Patient

Question	Answer	Code	Code* Weighting	Score
Likert Pain Intensity (scores)	4	2	2*0.4	0.8
	3			
	2	1	1*0.4	0.4
	1	0	0*0.4	0
	0			
Likert Pain Relief (scores)	4	0	0*0.4	0
	3			
	2	1	1*0.4	0.4
	1	2	2*0.4	0.8
	0			
Adverse events since the last consultation (number)	6 or more	2	2*0.2	0.4
	2–5	1	1*0.2	0.2
	0–1	0	0*0.2	0
Go to emergency department due to Pain	Yes	2	2*0.1	0.2
	No	0	0*0.1	0
VAS QoL (mm)	0–39	2	2*0.4	0.8
	40–70	1	1*0.4	0.4
	71–100	0	0*0.4	0
Range score **Cut-off limits**				**0–3** **1.2, 2.2**

Notes: The weightings are the component score coefficients estimated in the PCA, and the cut-off limits used were 1.2 respectively 2.2.

https://doi.org/10.2147/JPR.S490442



		PCA component groups (cut-off groups)		
		Green	Orange	Red
Cluster classes	0	57	27	0
	1	10	156	29
	2	0	9	130

Figure 3 The PCA component values are separated to a large extent by the cluster classes (up). Cross-tabulation of cluster classes and cut-off groups based on PCA component (bottom).

the component) were 0.8 for Likert pain intensity and pain relief, 0.7 for VAS QoL, 0.4 for number of AEs, and 0.2 for ED visits due to Pain.

To construct the component from the questionnaire data for the 5 items, the component score coefficients are needed. From the principal component analysis, they were for Likert pain intensity, pain relief and VAS QoL 0.4, number of AEs 0.2 and for ED visits due to Pain 0.1. To define cut-off points for the PCA dimension it was compared to the cluster classes, see the boxplot in Figure 3 (top). The cut-offs, 1.20 and 2.24, were based on the 10% percentile of the cluster class 1 and the 10% percentile of cluster class 2. This defined three groups based on the PCA component, to discriminate between three levels of burden of pain connected to clinical action. The agreement of these three levels of burden of pain was compared to the three cluster classes, with a percentage of agreement of 82%, see Figure 3 (bottom) in the cross-tabulation).

Differences Between Clusters

Clinical and pharmacological variables were analyzed among the three clusters to identify potential differences. All the results can be seen in Supplementary Table 3S. Consequently, we detected statistical differences concerning intensive monitoring, with patients from cluster 1 showing the highest frequency (cluster 0 24% vs cluster 1 27% vs cluster 2 20%, p-value < 0.05).

Regarding clinical variables, significant differences were observed in pain intensity. Specifically, statistically significant differences were noted in the basal visit between patients from clusters 1 and 2 (60 ± 16 vs 80 ± 15, p-value < 0.05) and patients from clusters 0 and 2 (48 ± 24 vs 80 ± 15, p < 0.0001). Significant differences were also observed in the final visit, where patients from cluster 2 referred the highest pain intensity: cluster 0 vs 1 (40 ± 25 vs 61 ±22, p-value < 0.01) and cluster 0 vs 2 (40 ± 25 vs 69 ± 17, p-value < 0.01). Furthermore, significant differences were also detected in the quality of life. In the basal visit patients from cluster 2 showed a worse quality of life compared to patients from cluster 0 (55 ± 20 vs 22 ± 23, p-value < 0.01) and from cluster 1 (48 ± 13 vs 22 ± 23, p-value < 0.01). These results indicate a poorer clinical response by patients from cluster 2.

Discussion

Results allow us to allocate patients to subgroups to receive an appropriate matched treatment and a stratified care, making in selecting the most appropriate level of care. These findings could serve to direct the approach taken specifically according to each specific situation and each person under CNCP. This can be usefully when the access to a physical examination is limited as teleassistance.

The results of this study could be compared with those obtained by other studies performed in a population with similar characteristics,[18] namely pain characteristics, psychological interference or other pharmacology/working status and impact of CNCP on daily life.[20] Although some of the variables mentioned in the above studies were included, another as ED visits or number of AEs has made it possible to establish groups of people based on the pain status impairment[13] without influence of sex, age or socio-economics impact. This could reduce the need for interventions within primary care and the risk of return to hospital because of unrelieved pain.[33]

To improve the management of CNCP health conditions, there is a need for models of care that can be widely implemented.[34] In fact, our data showed a significant impact in cluster 2 at basal that could deserve a different intervention for a better improvement. It is well known that the spectrum of pain ranges significantly from low risk, where an individual can deal with their own pain as a manageable condition with continued support, to higher risk individuals who require complex case-management programs. If the initial step only includes, eg, self-management advice, more people are potentially being undertreated with a staged approach than by risk stratification. By contrast, where more comprehensive core treatment packages are the initial level of care (eg, including pain medication), there is a risk of overtreatment and AEs in patients who would improve sufficiently with self-management advice alone. The likelihood that patients are overtreated or undertreated with risk-stratified care depends on the accuracy with which patients benefiting from more intensive care can be identified.[35,36] Our analysis was based on six clinically relevant states, converted into three CNCP risk subgroups, through simple algorithms constructed by two-step clustering, and PCA methods. Exploring the generalizability of models of care across conditions would inform clinicians about ways of developing care models and may facilitate implementation in clinical practice.

One of our data strengths is that our results provide real-world information about CNCP patients. These were: 68% middle-aged women, retired, under moderate pain and quality of life, and with a median of the five most typical AEs in pain management. We also performed some exploratory analysis about how some demographic variables could induce differences in GPSq as sex, age or incomes without any clear difference in the clusters.[37,38] What's more, pain intensity is therefore widely assessed plus other clinical outcomes. It has been suggested that the pain score (Numeric Rating Scale, NRS) 5 was the cut-off point between "manageable and not manageable pain"[39,40] similar to our mean pain intensity as one of the core outcome domains in clinical pain research.[41]

In addition to an accurate screening tool, better outcomes rely on there being suitably effective treatment options available for each risk stratum. Here, we found a six-cluster solution: little pain status with low interference with quality of life (Group 0, cluster 1); middle pain intensity, relief, quality of life impairment with variable adverse events (Group 1, Cluster 1–3); and high-risk patients with pain intensity, lower pain relief, in one case with poor drug tolerability due to the number of adverse events (Group 2, Cluster 4–5). The main focus of therapy for these patients should be close monitoring, because they could be highly distressed. The worst pain status is related to Cluster 5 due to their poorest quality of life and drug tolerance. Here, intense monitoring should be addressed with opioid rotation, referring patients to clinical sessions or to other specialists. Therefore, knowing the profiles of people with CNCP can help health staff to avoid worsening or derived complications, costs and ED visits.[42]

Finally, we must acknowledge the limitations of this study. Firstly, although the sample size was representative of this type of patients in our environment, due to inherent limitations, such as recruitment challenges or data heterogeneity and the generalization of the results. Larger samples are recommended to confirm the findings. Moreover, knowing that the GPSq is a new instrument that has been developed based on retrospective data from a single center where cause-effect relationships cannot be established. Therefore, these results should be handled with caution and would need future prospective studies in different settings and populations. In fact, a Swedish version has been designed for future studies. Besides, it has been conducted in a single-center of a specific region of Spain and in a one-time pain consultation.

Secondly, most patients were either on other non-opioid centrally acting drugs or presented other concomitant prescriptions (dosage, treatment duration, treatment adherence and non-pharmacological interventions) due to their comorbidities, which might have independently contributed to the side effects observed. This could introduce a bias mediated by several other variables, such as comorbidities, concomitant use of medications and psychosocial factors, mental status, that could be more relevant than pain. All this information would provide a better understanding of CNCP daily life impact which, together with other clinical outcomes (pain ethology, psychiatric illness, or co-medications use), could help us to design more individualized monitoring strategies.[35]

Conclusion

Briefly, the present study has identified three groups of CNCP patients that would require different pain management. The identification of distinct patient groups enables more personalized interventions, improving quality of life for high-risk patients and optimizing resource allocation for low-risk patients, which can reduce healthcare costs and unnecessary treatments. People with pain should be risk assessed at an early stage and referred to specialist pain management services to improve outcomes based on: (1) greater precision of risk assessment and individualized treatment that could be facilitated by GPSq, (2) greater patient agency through self-care/community-based care, and (3) more advanced training of primary care clinicians to be aware of risk factors for development of complex chronic pain, implement timely optimization of pain medication (monitoring for effectiveness, safety, intercurrent illness, and comorbidities), and instigate timely referral to specialist multidisciplinary pain management services. Future prospective and external validation is necessary to confirm this pain patient´s stratification being able to promote the generalizability in different settings, such as primary care.

Ethic Statement

The study is observational with a retrospective nature, making it practically impossible to obtain informed consent from all participants. Therefore, the requirement for individual consent was waived by the Ethics Committee of Alicante-General Hospital, which is part of the ISABIAL health organization. All patient data were anonymized and handled in strict compliance with the principles of confidentiality, adhering to the Declaration of Helsinki and applicable regulations.

Acknowledgments

The authors would like to thank Mrs. Fernanda Jiménez and Mrs. Andrea Flor (Nurses, PU, Alicante General Hospital), and the senior researchers: Dr. Raquel Ajo, Dr. Pura Ballester and Dr. Beatriz Planelles (for the initial support with the validation GPSq study), and M-del-Mar Inda (Senior researchers, Alicante General Hospital) for their assistance in formatting the protocol research GPSq validation. Thanks to Julissa Guerrero, MD for the support in the retrospective data assessment.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hardt J, Jacobsen C, Goldberg J, Nickel R, Buchwald D. Prevalence of Chronic Pain in a Representative Sample in the United States. *Pain Med*. 2008;9(7):803–812. doi:10.1111/j.1526-4637.2008.00425.x
2. European Pain Federation. *Pain and Mental Health in Europe*; 2023.
3. Rios R, Zautra AJ. Socioeconomic disparities in pain: the role of economic hardship and daily financial worry. *Health Psychol*. 2011;30(1):58–66. doi:10.1037/a0022025
4. Liang Y. Life course socioeconomic status, chronic pain, and the mediating role of allostatic load: findings from the midlife in the United States. *Front Public Health*. 2024;12:1365105. doi:10.3389/fpubh.2024.1365105
5. Bach-Rojecky L, Vađunec D, Žunić K, et al. Continuing War on Pain: a Personalized Approach to the Therapy with Nonsteroidal Anti-Inflammatory Drugs and Opioids. *Per Med*. 2019;16(2):171–184. doi:10.2217/pme-2018-0116
6. Fogelman Y, Carmeli E, Minerbi A, Harash B, Vulfsons S. Specialized Pain Clinics in Primary Care: common Diagnoses, Referral Patterns and Clinical Outcomes – novel Pain Management Model. *Clin Investigat*. 2017;2017:89–98. doi:10.1007/5584_2017_108
7. Faculty of Pain Medicine. *Core Standards for Pain Management Services in the UK*. 2021;Vol. 2021.
8. Spooner L, Fernandes K, Martins D, et al. High-Dose Opioid Prescribing and Opioid-Related Hospitalization: a Population-Based Study. *PLoS One*. 2016;11(12):e0167479. doi:10.1371/journal.pone.0167479

9. Upp LA, Waljee JF. The Opioid Epidemic. *Clin Plast Surg*. 2020;47(2):181–190. doi:10.1016/j.cps.2019.12.005
10. Hill JC, Garvin S, Bromley K, et al. Risk-based stratified primary care for common musculoskeletal pain presentations (STarT MSK): a cluster-randomised, controlled trial. *Lancet Rheumatol*. 2022;4(9):e591–e602. doi:10.1016/S2665-9913(22)00159-X
11. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic Factor Research. *PLoS Med*. 2013;10(2): e1001380. doi:10.1371/journal.pmed.1001380
12. Furlan AD, Reardon R, Weppler C. Opioids for chronic noncancer pain: a new Canadian practice guideline. *Can Med Assoc J*. 2010;182 (9):923–930. doi:10.1503/cmaj.100187
13. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain. *JAMA*. 2018;320(23):2448. doi:10.1001/jama.2018.18472
14. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. *JAMA Intern Med*. 2017;177(8):1146. doi:10.1001/jamainternmed.2017.1622
15. Barrachina J, Muriel J, Margarit C, et al. Global Pain State Questionnaire: reliability, Validity, and Gender Gap. *Archi Int Med Res*. 2021;04(02). doi:10.26502/aimr.0061
16. Sowden G, Hill JC, Morso L, Louw Q, Foster NE. Advancing practice for back pain through stratified care (STarT Back). *Braz J Phys Ther*. 2018;22(4):255–264. doi:10.1016/j.bjpt.2018.06.003
17. Paul SM, Zelman DC, Smith M, Miaskowski C. Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. *Pain*. 2005;113(1):37–44. doi:10.1016/j.pain.2004.09.014
18. Dueñas M, Salazar A, Ojeda B, et al. A Nationwide Study of Chronic Pain Prevalence in the General Spanish Population: identifying Clinical Subgroups Through Cluster Analysis. *Pain Med*. 2015;16(4):811–822. doi:10.1111/pme.12640
19. NHS England Specification. *Adult Highly Specialist Pain Management Services*. 2019.
20. Cáceres-Matos R, Gil-García E, López-Millán JM, Martínez-Navas Á, Peña I, Cabrera-León A. Profiles of adult people in a Spanish sample with chronic pain: cluster analysis. *J Adv Nurs*. 2022;78(9):2837–2848. doi:10.1111/jan.15201
21. Jensen MP, Karoly P. *Self-Report Scales and Procedures for Assessing Pain in Adults*. 3rd ed. Guilford Press; 2011.
22. Planelles B, Margarit C, Ajo R, et al. Health benefits of an adverse events reporting system for chronic pain patients using long-term opioids. *Acta Anaesthesiol Scand*. 2019;63(2):248–258. doi:10.1111/aas.13243
23. Herdman M, Badia X, Berra S. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Aten Primaria*. 2001;28(6):425–429. doi:10.1016/S0212-6567(01)70406-4
24. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;10(10):CD012509. doi:10.1002/14651858.CD012509.pub2
25. Sino CG, Stuffken R, Heerdink ER, Schuurmans MJ, Souverein PC, Egberts TC. The association between prescription change frequency, chronic disease score and hospital admissions: a case control study. *BMC Pharmacol Toxicol*. 2013;14(1):39. doi:10.1186/2050-6511-14-39
26. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the Management of Chronic Severe Pain in the Elderly: consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone). *Pain Pract*. 2008;8(4):287–313. doi:10.1111/j.1533-2500.2008.00204.x
27. Justins DM. The faculty of pain medicine of the Royal College of Anaesthetists. *Br J Anaesth*. 2008;101(1):4–7. doi:10.1093/bja/aen104
28. Cabrera-León A, Rueda M, Cantero-Braojos M. Calibrated prevalence of disabling chronic pain according to different approaches: a face-to-face cross-sectional population-based study in Southern Spain. *BMJ Open*. 2017;7(1):e014033. doi:10.1136/bmjopen-2016-014033
29. Barrachina J, Margarit C, Muriel J, et al. Oxycodone/naloxone versus tapentadol in real-world chronic non-cancer pain management: an observational and pharmacogenetic study. *Sci Rep*. 2022;12(1):10126. doi:10.1038/s41598-022-13085-5
30. Matamalas A, Ramírez M, Mojal S, et al. The Visual Analog Scale and a Five-Item Verbal Rating Scale Are Not Interchangeable for Back Pain Assessment in Lumbar Spine Disorders. *Spine*. 2010;35(21):E1115–E1119. doi:10.1097/BRS.0b013e3181e7b315
31. Benassi M, Garofalo S, Ambrosini F, et al. Using Two-Step Cluster Analysis and Latent Class Cluster Analysis to Classify the Cognitive Heterogeneity of Cross-Diagnostic Psychiatric Inpatients. *Front Psychol*. 2020;11:1085. doi:10.3389/fpsyg.2020.01085.
32. Kent P, Jensen RK, Kongsted A. A comparison of three clustering methods for finding subgroups in MRI, SMS or clinical data: SPSS TwoStep Cluster analysis, Latent Gold and SNOB. *BMC Med Res Methodol*. 2014;14(1):113. doi:10.1186/1471-2288-14-113
33. Royal College of Anaesthetists. *Chapter 11: Guidelines for the Provision of Anaesthesia Services for Inpatient Pain Management*. 2022.
34. Kongsted A, Kent P, Quicke JG, Skou ST, Hill JC. Risk-stratified and stepped models of care for back pain and osteoarthritis: are we heading towards a common model? *Pain Rep*. 2020;5(5):e843. doi:10.1097/PR9.0000000000000843
35. Hancock M, Herbert RD, Maher CG. A Guide to Interpretation of Studies Investigating Subgroups of Responders to Physical Therapy Interventions. *Phys Ther*. 2009;89(7):698–704. doi:10.2522/ptj.20080351
36. Kongsted A, Hestbæk L, Kent P. How can latent trajectories of back pain be translated into defined subgroups? *BMC Musculoskelet Disord*. 2017;18(1):285. doi:10.1186/s12891-017-1644-8
37. Robinson ME, Gagnon CM, Dannecker EA, Brown JL, Jump RL, Price DD. Sex differences in common pain events: expectations and anchors. *J Pain*. 2003;4(1):40–45. doi:10.1054/jpai.2003.4
38. Robinson ME, George SZ, Dannecker EA, et al. Sex differences in pain anchors revisited: further investigation of "most intense" and common pain events⋆. *Eur. J. Pain*. 2004;8(4):299–305. doi:10.1016/j.ejpain.2003.10.003
39. Zelman DC, Dukes E, Brandenburg N, Bostrom A, Gore M. Identification of cut-points for mild, moderate and severe pain due to diabetic peripheral neuropathy. *Pain*. 2005;115(1):29–36. doi:10.1016/j.pain.2005.01.028
40. Dihle A, Helseth S, Paul SM, Miaskowski C. The Exploration of the Establishment of Cutpoints to Categorize the Severity of Acute Postoperative Pain. *Clin J Pain*. 2006;22(7):617–624. doi:10.1097/01.ajp.0000210905.57546.c1
41. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113 (1):9–19. doi:10.1016/j.pain.2004.09.012
42. Higgins C, Smith BH, Colvin L. Examination of the clinical factors associated with attendance at emergency departments for chronic pain management and the cost of treatment relative to that of other significant medical conditions. *Pain*. 2021;162(3):886–894. doi:10.1097/j.pain.0000000000002098