

Research Article

Global Pain State Questionnaire: Reliability, Validity, and Gender Gap

Jordi Barrachina¹, Javier Muriel¹, Cesar Margarit^{1, 2}, Beatriz Planelles¹, Pura Ballester¹, Miguel Richart-Martínez³, Esperanza Cutillas⁴, Thomas Zandonai^{5, 6}, Domingo Morales⁷, Ana M Peiró^{1, 2, 8*}

¹Neuropharmacology on Pain and Functional Diversity, Institute of Health and Biomedical Research of Alicante, Alicante, Spain

²Pain Unit, Department of Health, Alicante-General Hospital, Alicante, Spain

³Department of Nursing, Faculty of Health Sciences, University of Alicante, Alicante, Spain

⁴Occupational Observatory, Miguel Hernández University of Elche, Elche, Spain

⁵Department of Clinical Pharmacology, Paediatrics and Organic Chemistry, Miguel Hernández University of Elche, Elche, Spain

⁶Mind, Brain and Behaviour Research Centre, Department of Experimental Psychology, University of Granada, Granada, Spain

⁷Operations Research Centre, Miguel Hernández University of Elche, Elche, Spain

⁸Clinical Pharmacology Unit, Department of Health, Alicante - General Hospital, Alicante, Spain

***Corresponding author:** Ana M Peiró, Clinical Pharmacology Unit, Department of Health of Alicante - General Hospital Calle Pintor Baeza 12, Alicante, Spain, Tel: 34-965.913.868; Fax: 913896

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Abstract

Objective: To quantify patients' pain more objectively is essential to guide an individualized therapy, all the more so in patients under long-term opioid-use. Only a

thoughtful and objective understanding of risks and benefits could improve an individualized standard of care. Our aim was to assess metric reliability and validity of an integrated and self-report Global Pain

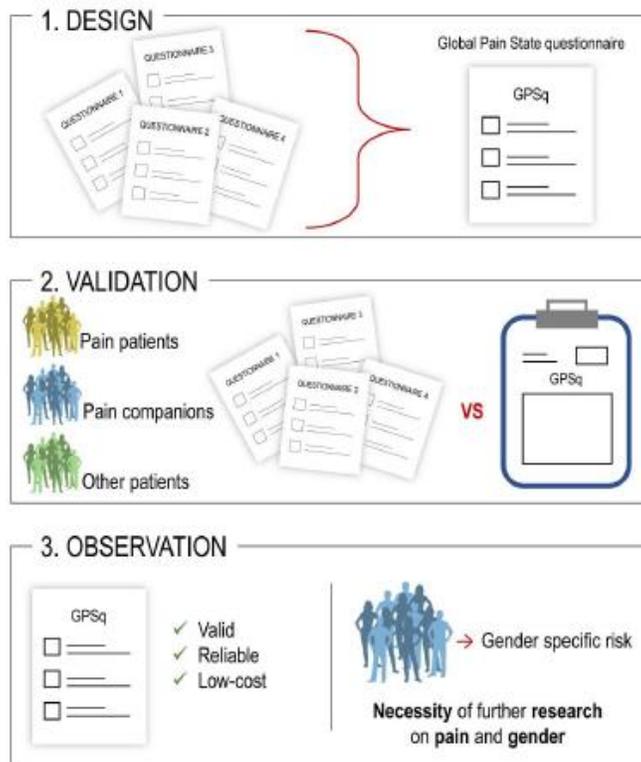
Status questionnaire to quantify the impact of pain on patient’s health in a more precise manner.

Methods: A cross-sectional study was conducted to analyse the reliability, agreement, and validity of an integrated questionnaire compared to isolated scales, due to kappa statistics, intra- class and other correlation coefficients. Level of pain (intensity and relief), quality of life, most prevalent analgesic adverse events and hospital frequentation were registered in a total of 38 cases (pain unit patients) and 52 painless matched-controls.. A reduced multitrait-multimethod matrix and a canonical-correlation analysis were developed together with a multiple linear regression.

Results: Cases (56 ± 10 years old, 63% females, pain intensity 66 ± 23 mm, incidence rate of 5 adverse events) represented a regular pain population. A high

intraobserver correlation ($r=0.75-0.88$, weighted- $\kappa=0.41-0.51$, unweighted- $\kappa=0.66-0.82$) was evidenced together with significant correlation coefficients in test-retest reliability, and for validity, even more, in a reduced multitrait-multimethod matrix (>0.8) and canonical-correlation (>0.95). A gender gap was evidenced in cases’ companions, mostly middle-aged females (78%), who experienced negative effects on their health.

Conclusions: The Global Pain Status questionnaire is an evaluation instrument with enough reliability and validity, being a low-cost method to determine the multidimensional pain management at clinical routine. A gender-gap within pain caregivers was found that affect their health outcomes. Support interventions for pain patients’ companions should consider specific gender risk factors.



Keywords: Reliability; Validity; Chronic Pain; Gender; Analgesic Response

Abbreviation: GPSq: Global Pain State questionnaire; CNCP: Chronic Non-Cancer Pain; AEs: Adverse Events; PC: Patients' Companions; PU: Pain Unit; CC: Clinical Units; VAS: Visual Analogue Scale; EQ: EuroQol; MEdDRA: Medical Dictionary for Regulatory Activities; ICC: Intraclass Coefficient Correlation; κ : Kappa; ANOVA: Analysis of Variance; IRB: Institutional Review Board

1. Introduction

Pain is the most common physical symptom that occurs in medicine representing a substantial burden for the individual patient and medical care [1]. However, pain as a multifaceted outcome is still an underestimated health problem with high interindividual variability in analgesic response [2]. One of the challenges when using opioids is to improve their safety profile, since it is still the leading cause of treatment abandonment [3]. Polypharmacy is very frequent in pain management and side effects that often are underestimated or misinterpreted as they may mimic underlying causes of pain co-morbid conditions [4], fostering a prescribing cascade [5]. Developing a better understanding of such differences and the mechanisms that support them is the basis for optimising pain treatment on an individual-by-individual focus. The first step for this understanding is the use of objective and validated tools to quantify the impact of pain on the patient's health in a more precise manner [6].

Nowadays, there are multiple instruments to assess chronic pain [7]. However, questionnaires separately assess effectiveness variables (pain and functional impact as in Brief Pain Inventory) and, on the other, pharmacological secondary effects such as UKU side effect rating scale. What's more, most of them are

“hardly likely to exploit the discriminative capacity of most people in terms of their perceived welfare” [8], are too restrictive, not self-reported, and require precious clinical time and they are thus scarcely used in standard pain care [9].

Therefore, there is a need for easy-to-use questionnaires that quickly check the patient's general pain status and analgesic side-effects, which reliably measures, and able to assess patients interindividual differences in clinical routine. What's more, instruments need to be easy to use and understand in order to facilitate patient's collaboration, saving time for the healthcare physicians. Hence, the possibility of using a self-report and integrated questionnaire that incorporates the most used and validated scales in pain management [10] would be interesting. The purpose of this study was to assess metric reliability – in terms of constancy and accuracy of the results on different occasions- and validity – in terms the degree to which an instrument measures the variable it has been designed for - of an integrated Global Pain Status questionnaire (GPSq) to be used in standard pain care.

2. Materials and Methods

2.1 Study design

A cross-sectional study was conducted at the Pain Unit of the Department of Health of Alicante-General Hospital (Alicante, Spain) from October 2015 to July 2016. Ethics Committee approved the study that was carried out following the ethical guidelines of the Declaration of Helsinki. This study was approved by the appropriate Institutional Review Board (IRB) and written informed consent was obtained from all subjects. This manuscript adheres to standardised questionnaire validation methods.

2.2 Participant selection

A consecutive sampling method was used open to

CNCP outpatients, in the waiting room, before any medical practice was conducted. Once a week during a month (from 10-12 a.m.), patients were informed about the purpose of the study. Interested individuals were asked to complete on their own a routine questionnaire consisting of clinical assessment measures (isolated questionnaires) and the integrated (GPSq) under study, with 10 minutes of washout period. Supplementary Material Figure 1 illustrates the GPSq questionnaire (Spanish and English versions). At the same time, researchers offer the possibility of participating in the study on pain unit outpatient painless matched-controls divided into two groups: a) patients' companions (PC) with potential common life style or dietary habits; and b) outpatient patients from another three clinical units (CC: cardiology, haematology, and orthopaedic surgeon). Inclusion criteria were: adult (≥ 18 years old), under long-term pain therapy at the PU (stable for six months or longer), previous diagnosis of CNCP verified by record review, according to medical standard care, an adequate mental status for properly filling in the scales and questionnaire, and agreement with verbal consent. Two control-matched groups (age, sex, and geographical area) comprising painless individuals included: PC (n=27, subjects from cases' companions) and CC (n=25, patients from three other clinical Units who usually collaborate with our Pain Unit). The exclusion criteria were people that do not fulfil inclusion criteria or an inability to complete the tasks.

2.3 Instrument design

GPSq items were selected through a multi-step process: 1) review of the existing literature about most frequently used validated scale suggested by the Spanish Pain Society; 2) patient interviews and focus group of 20 patients in a PU outpatient environment (these patients were selected two weeks before recruitment started); 3) examination by the research group of the focus group; 4) item writing and selection revised by the group; and

5) examination of the inventory by seven independent experts in pain management, for content validity. This questionnaire was used at previous research projects in a different set of pain patients at our PU [10, 11].

2.4 Variables

After verbal consent to participate, questionnaires were self-administered under the supervision of a researcher, assessing socio-demographic (age, gender, height, weight, employment situation, and education level), clinical and safety pain-related variables [12].

2.4.1 Clinical variables: A hard copy version of the Visual Analogue Scale (VAS), consisting of a 100mm horizontal line anchored by two extremes, where 0 means "no pain" and 100mm is "worst pain imaginable", and a 5-scores Likert categorical scale were full fight from 0 "none", 1 "mild", 2 "moderate", 3 "severe" and 4 "extremely severe pain" [13] were used to record pain intensity and relief [14, 15]. Quality of life was registered due to EQ-VAS (0-100mm) and EQ-5D questionnaire (maximum value is 1 "best" and 0 "worst" state of health imaginable), it includes five questions regarding mobility, personal care, daily activities, pain and anxiety/depression dimensions, that allows us to obtain the final score [16].

2.4.2 Safety variables: Patients were encouraged to report all AEs in which pain medication was suspected (anoxious, unintended, or undesired effect of a drug that occurs at dosages used in humans for prophylaxis, diagnosis, or therapy). Most frequent opioid AEs were listed including open fields for patients to include any other. All reports were classified following the Medical Dictionary for Regulatory Activities (MedDRA) for the coding of clinical data in AEs reports [17]. Even more, hospital admission, frequentation, and drug prescription change (due to pain or other reasons) were asked.

2.5 Procedures

The completion of isolated scales and GPSq was performed in the clinical units to which participants belonged, administered in a random order following sequence: A (first GPSq, second control-isolated scales) and B (opposite order). Test-retest reliability was examined 10 minutes apart, firstly one questionnaire and after that period, patients must complete the next. This short time was fixed in an effort to capture a constant pain level [18]. All were registered in a single session lasting 15 minutes. Each study participant was provided with instructions by four researchers who had a previous experience minimum of six months in medical pain routine. Hence, intra-observer reliability was evaluated.

2.6 Reliability evaluation

Reliability was measured according to the maintenance of constancy in participants' answers [19] in a minimum sample size of 35 participants. This was calculated based on parameter estimation of an intra-class correlation coefficient (ICC, 0.85, 95% CI with of 0.20 scores) and a 10% loss to follow-up. Intra-rater reliability, a metric for rater's self-consistency, was used to assess in a continuous clinical measurement [20]. It is considered as reproducible if the same rater, under the same conditions and with repeated scores, shows a non-significant rater variation [21].

2.6.1 Cohen's kappa coefficient for categorical variables:

This κ coefficient measures agreement between two raters (intra-rater reliability) who classify N items into C mutually exclusive categories in categorical variables (Likert pain and relief intensity). Weighted κ coefficient is related to the level of disagreement between raters, whilst unweighted κ coefficient indicated how different the scores are. κ values range between -1 ("no agreement") and 1 ("complete agreement"). Thus, correlation can be "poor"

(κ between -1 and 0), "slight" (0.01-0.2), "fair" (0.21-0.4), "moderate" (0.41-0.6), "substantial" (0.61-0.8) or "almost perfect" (0.81-1).

2.6.2 Intraclass correlation coefficient (ICC) for continuous variables:

This is a measurement of the total variance of the sample, which includes the differences among raters, subjects, and the unexplained residual variance. Both, ICC and weighted- κ scores may be interpreted according to the following values: "chance" (0), "poor" (0 to 0.19), "fair" (0.20 to 0.39), "moderate" (0.40 to 0.59), "substantial" (0.60 to 0.79), and "almost perfect" (0.80 to 1.0) agreement [22].

2.7 Validity evaluation

2.7.1 Responsiveness or sensitivity to change:

This is the ability of an instrument to detect changes in the attribute or variable that is measured over time and related to the magnitude of the difference in the subject's scores [23]. To assess the responsiveness, effect size technique was performed. Cramer's V considered values were <0.07 "small", >0.21 "medium" and >0.35 "large". Eta-squared considered values were <0.02 "small", >0.13 "medium" and >0.26 as a "large" effect.

2.7.2 Content validity:

Questionnaire items were selected initially by two pain unit anaesthesiologist clinicians (CM, LG), two clinical pharmacologists (JH, AP), two pharmacists (JM, PB) and one biotechnologist (BP) as a group of experts due to: clarity (easily understood), coherence (related with that which it is intended to evaluate), relevance (to evaluate that which is intended) and sufficiency (to fully assess that which is intended). Half the experts account for more than 20 years of healthcare, teaching, and research experience [24].

2.7.3 Criterion validity-correlation: Correlations were assessed using Spearman's (non-parametric variables) or Pearson's (parametric variables). Paired two-sided student's t-tests were used for a comparison of the means of normally distributed parameters. A "moderate" (>0.5) or "strong" (>0.7) correlation were considered. Given the direction of the scales, VAS pain intensity was expected to demonstrate a "strong" negative correlation ($r \geq -0.70$) with VAS pain relief and a "moderate" negative correlation ($r \geq -0.40$) with VAS quality of life. In the same way, a "moderate" to "strong" positive correlation ($r \geq 0.50$) would be expected between VAS pain relief and VAS quality of life.

2.7.4 Construct validity: An instrument is validated when it correlates with another through variables that should be related. The unrelated ones can be obtained with (i) known-groups validity that is a type of construct validity which measures the ability of an instrument to distinguish and between different groups [25], and (ii) convergent and divergent validity that evaluates the sensitivity and the divergent specificity of the instrument [26].

2.7.5 Reduced multitrait-multimethod matrix: It was performed to provide evidence of validity about the pain and quality of life items to prove convergent and divergent hypotheses through three concepts (pain intensity, relief, and quality of life) and two methods (VAS and Likert). In this type of matrix, convergent validity refers to the fact that the correlation between the same trait (e.g. pain intensity) with a different method (e.g. VAS or Likert) will show the highest correlations [25]. Values >0.5 will be considered "moderate" and >0.7 "strong" correlation.

2.7.6 A canonical-correlation analysis: The Common between two sets of variables was calculated to infer

information from *cross-covariance matrices*. This analysis will try to find linear combinations of the two vectors $X(\text{case}) = (X_1, \dots, X_n)$ and $Y(\text{control}) = (Y_1, \dots, Y_m)$ which have a maximum correlation with each other. Data is showed by plotting them as heliographs, a circular format with ray-like bars, with each half representing the two sets of variables for better visualisation.

2.8 Statistical analysis

Sample size was calculated due to 10 participants per item evaluated as described in other studies [27]. Therefore, at least 50 subjects were required for the five-items (VAS pain intensity, relief, and quality of life; 5-Likert points for pain intensity and relief). The assumption of normality was tested with the Kolmogorov Smirnov test with the correction of Lilliefors. Data were expressed as mean \pm standard deviation or as median (P25-P75) for parameters with non-normal distribution. Whether two groups were compared, differences for numerical or ordinal data were evaluated with T-test or Mann-Whitney test, and one-way analysis of variance or Kruskal-Wallis ANOVA-test whether we compared three groups, according to normality. χ^2 and Fisher's Exact test were used to compare groups for categorical data, depending on whether two or three groups were analysed. The effect size was calculated. Multiple linear regression was carried out to analyse the influence of the following factors: pain intensity, quality of life, age, sex, and number of AEs over pain relief. Floor and ceiling effects were performed, defined as the percentage of patients with the lowest and highest score in the categorical variables (Likert pain intensity and relief). The alpha level that defines statistical significance was 0.05 ($p\text{-value} < 0.05$). Statistical analyses were performed on R 3.2.0.

3. Results

A total of 65 patients pre-screened at the Alicante

Hospital Pain Unit met the inclusion criteria, of which 52 agreed to participate. Of the latter, 14 patients were excluded as some data on the questionnaires were

missing. Thus, 38 cases and all controls finished the study (PC control group n=27, CC control group n=25) (Figure 1).

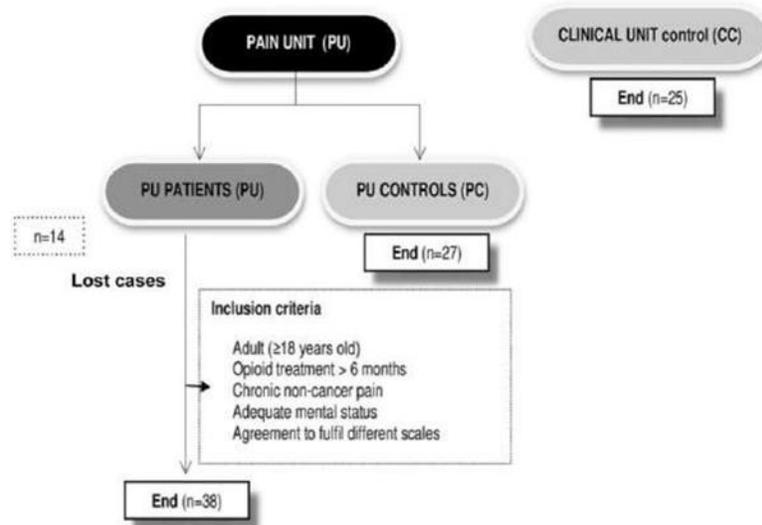


Figure 1: Flow chart.

3.1 Participant

Demographic, clinical, and safety data are reported in Table 1. Participants were mainly middle-aged (range 56-65 years) women (63-78%), with secondary school certificate (more than 45%) and retired (48-65%). Participants were predominantly female representing 78% of cases companions. No other differences were observed in the other demographic variables registered in the present study.

3.2 Clinical variables

As expected, cases showed the highest significant pain intensity (66 ± 23 mm) compared to controls (PC and CC, 44 ± 20 and 41 ± 29 mm, p -value= <0.0001) with a large effect size (0.243). Cases and their PC companions showed similar scores for VAS pain relief (mean range 39-41 mm) and significantly different from CC (65 mm, $p < 0.05$). Furthermore, the CC group showed the highest EQ-5D quality of life (0.68 ± 0.23 scores) with differences around 0.20 scores from PU and PC (p -Archives of Internal Medicine Research

value=0.0064, effect size=0.257), mostly related to mobility and pain areas (Supplementary Material Table 1). Thus, caregivers showed lower quality of life outcomes than patients from other clinical units (PC vs. CC, 0.51 ± 0.24 vs 0.68 ± 0.23 , p -value=0.0064, effect size=0.257). Cases and their companions showed similar hospital services use rates but significantly different from CC related to hospital frequentation. They visited more frequently emergency room (PU, PC and CC, 27%, 16% and 0%, respectively, p -value=0.008, large effect size=0.38) with higher hospital admission rates (25%, 21% and 0%, respectively, p -value=0.006, large effect size=0.49).

3.3 Safety variables

Table 2 and Supplementary Material Figure 2 illustrated a total of 247 AEs registered in the study. Half of the cases demonstrated almost one AE (incidence rate 5 AEs/case) with a median AEs number of 2 (IQR, 1-5). This was significantly higher than controls (p -

value=0.031, effect size=0.144) and in a similar range than our typical PU population [28]. Cases vs. control (PC-CC) showed a significant higher degree of xerostomia (50% vs. 0-15%, p-value=<0.0001), constipation (39% vs. 8-15%, p-value=0.0195), dry skin (29% vs. 4-15%, p-value=0.043) and somnolence (23% vs. 0-18%, p-value=0.0192). It is interesting to point out that all participants suffer from a similar prevalence of insomnia (20-25%), depression (15- 17%). Furthermore, a consistent high prevalence was found for cases and their companions vs. CC in weight change (15-23 vs. 8%), loss of appetite (10-21 vs. 4%), edema (13-15% vs. 0%) and loss of libido (5-6 vs. 0%).

3.4 Multiple linear regression

Cases and their companions did not show any statistically significant relation of some variables (pain intensity, quality of life, age, sex, and number of AEs) over their pain relief. However, the CC group evidenced a negative correlation of pain relief with pain intensity and a positive correlation with the quality of life (Supplementary Material Table 2).

3.5 Reliability analysis

Results showed high intra-observer reliability and agreement between GPSq and isolated scales (Table 3). Substantial agreement was found between VAS pain intensity (>0.7), relief (>0.8), and quality of life (EQ-VAS 0.88; EQ-5D 0.86). The agreement of Likert pain intensity achieved a moderate weighted- κ coefficient (0.41, the limit of an acceptable correlation), but also a substantial unweighted- κ (0.66). Furthermore, Likert pain relief obtained a moderately weighted- κ (0.51) and an almost perfect unweighted- κ (0.82).

3.6 Validity analysis

3.6.1 Responsiveness or sensitivity to change: Results suggested GPSq good responsiveness through effect size (Table 1). A large effect size was evidenced in pain

intensity (VAS, 0.243), quality of life (EQ-5D, 0.257), and number of AEs (0.144). Furthermore, a medium effect size in sex (0.124) and pain relief (0.093) was found according to the expected differences between groups.

3.6.2 Content validity: Experts chose the items that formed the GPSq questionnaire due: easy to understand (clarity), able to evaluate pain intensity adequately (related to that which it is intended to evaluate). Besides, the items were isolated used in our population showing good results (essential to evaluate what is intended) and allowing an idea of the patient's state of pain to be obtained (enough to fully assess that which is intended) [29, 30].

3.6.3 Criterion validity-correlation: Table 4 represents the intra-rater correlation between the GPSq questionnaire and isolated scales. Spearman correlation coefficients (pain scores and quality of life) ranged from 0.72 to 0.90, Spearman correlation coefficients (pain scores and quality of life) ranged from 0.72 to 0.90, in this case, Spearman correlation was used, since both variables did not comply with the assumption of normality. It has been found that when VAS pain intensity increased, a decreased score was found for: (i) pain relief at a moderate level (GPSq [r =0.52], isolated scales [r=0.35], and both [r=0.29]); and (ii) quality of life at a mild level (r=0.22, r=0.21 and r=0.28, respectively). This VAS pain intensity increases and also associated Likert pain intensity increase to a strong degree (r=0.81, r=0.83, and r=0.75, respectively). Furthermore, GPSq VAS pain relief increases induce a quality of life increase to a moderate degree (r=0.45). On the other hand, the correlation between GPSq and isolated scales regarding the same variables were high at pain intensity (VAS [r=0.91], Likert [r=0.9]) and pain relief (VAS [r=0.82], Likert [r=0.83]). The highest correlation was found for the quality of life (EQ-VAS [r=0.88], EQ-5D [r=0.98]). Thus, participants did not

change their answers depending on the scale (GPSq or the isolated ones).

Self-Reportedey Pantients				
Population	Case	Control		P-value
Variables	PU (n=38)	PC (n = 27)	CC (n = 25)	
Sex (female, %)	63	78*X	65	.031 ^a .124 ^I
Age, mean (SD), yeas old	56 (10)	65 (15)	62 (15)	.268 ^b .09 ^{II}
Pain intensity, mean (SD), VAS mm	66 (23)***	44 (20)	41 (29)	.000 ^{1b} .243 ^{III}
Pain relief, mean (SD), VAS mm	41 (28)++	39 (23)XX	65 (26)	.0005 ^b .093 ^{III}
Likert pain intensity (%)				
None	0	0	12	.417 ^c
Mild	11	26	24	3.8 ^I
Moderate	44	39	12	10 ²
Severe	37	26	20	.35 ^I
Extreme severe	11	9	16	
Likert pain relief (%)				
EQ-VAS, mean (SD), mm	52 (21)	57 (18)	60 (25)	.852 ^b .003 ^{III}
EQ-5D, score, mean (SD)	0.48 (0.19)	0.51 (0.24)	0.68 (0.23)	.0064 ^d .257 ^{III}
Adverse Events, median [IQR]	2 [1-5]**	1.5 [0-3]	1 [0-2]	.031 ^e .144 ^{III}
Due to pain				
Emergency visit (%)	11	5	4	.082 ^a .255 ^I
Hospital admission (%)	8	5	4	.677 ^a .066 ^I
Change of drug (%)	21	16	8	.193 ^a .36 ^I
Due to other causes				
Emergency visit (%)	27++	16X	0	.008 ^a .38 ^I
Hospital admission (%)	25++	21XX	0	.006 ^a .49 ^I

Change of drug (%)	9	7	0	.134 ^a
				.23 ¹

Note: SD: Standard Deviation; IQR: Interquartile Range; VAS: Visual Analogue Scale; EQ-VAS: EuroQol scale; EQ-5D: EuroQol-5D. P-value < 0.05 is written in bold font. Cases vs. controls (PC and CC): p-value * < 0.05, ** p-value < 0.01, p-value *** < 0.001 Cases vs. control (CC): ⁺p-value < 0.05, ⁺⁺p-value < 0.01, Control PC vs. CC: ^xp-value < 0.05, ^{xx}p-value < 0.01

¹ Floor effect (%) patients with the lowest score; ² Ceiling effect (%) patients with the highest score.

^a Fisher's exact test; ^b One-way ANOVA; ^c Chi-Square Test; ^d Kruskal-Wallis test; ^e Mann-Whitney Test. Estimation of Effect size: ^I Cramer's V; ^{II} Eta squared for One-Way ANOVA; ^{III} Eta squared for Kruskal Wallis Test.

Table 1: Demographic, clinical and pharmacological data related to cases (pain unit patients, PU) and controls (patients' relatives (PC) and patients from other clinical units (CC)).

Adverse events (%)	Case	Control		P-value
	PU (n = 38)	PC (n = 27)	CC (n = 25)	
Xerostomia	50***	15	0	<0.001
Constipation	39**	15	8	0.0195
Dizziness	35	10	16	0.1366
Dry skin	29*	15	4	0.043
Headache	29	10	12	0.2036
Somnolence	23 ⁺⁺	18 ^{xx}	0	0.0192
Insomnia	23	25	20	0.4268
Weight change	23	15	8	0.262
Loss of appetite	21	10	4	0.1509
Depression	17	15	16	0.9808
Nervousness	16	15	0	0.068
Pruritus	13	0	4	0.1874
Nauseas	13	5	4	0.4129
Edema	13	15	0	0.1492
Vomiting	10	5	0	0.2816
Erectile dysfunction	8	0	0	0.2166
Loss of libido	6	5	0	0.4273
Erythema	4	0	0	0.4736
Incidence rate AE/patient	5	2	0.5	0.3294

Control PC vs. CC: ^xp-value < 0.05, ^{xx}p-value < 0.01, P-values < 0.05 are written in bold font. P-values were obtained through Chi-square test. Cases vs. controls (PC and CC): p-value * < 0.05, ** p-value < 0.01, p-value *** < 0.001 Cases vs. control (CC): ⁺p-value < 0.05, ⁺⁺p-value < 0.01⁺⁺

Table 2: Frequency of adverse events self-reported by cases (pain unit patients, PU) and controls (patients' relatives (PC) and patients from other clinical units (CC)).

Clinical variable	Scale	Reliability test-retest
Pain intensity	VAS	0.76 ¹
	Likert	0.41 ² / 0.66 ³
Pain relief	VAS	0.81 ¹
	Likert	0.51 ² / 0.82 ³
Quality of life	VAS	0.88 ¹
	EQ-5D	0.86 ¹

VAS: Visual Analogue Scale (0-100 mm); EQ-5D: EuroQol-5D (0-1 score)

¹ Intraclass Correlation Coefficient; ² weighted Kappa; ³ unweighted Kappa.

Table 3: Reliability of test-retest analysis. Results of Intraclass Correlation Coefficient (ICC) for continuous variables, and Cohen's Kappa (weighted and unweighted) for continuous variables.

Correlations between GPSq scales							
		Pain intensity		Pain relief		Quality of life	
		VAS	Likert	VAS	Likert	VAS	EQ-5D
Pain intensity	VAS	1,000	0,814	-0,529	-0,554	-0,217	-0.373
	Likert	0,814	1,000	-0,531	-0,527	-0,165	-0.528
Pain relief	VAS	-0,529	-0,531	1,000	0,912	0,446	0.531
	Likert	-0,554	-0,527	0,912	1,000	0,469	0.47
Quality of life	VAS	-0,217	-0,165	0,446	0,469	1,000	0.494
	EQ-5D	-0,373	-0.528	0.531	0.47	0.494	1
Correlations between isolated scales							
Pain intensity	VAS	1,000	0,833	-0,346	-0,515	-0,214	-0.244
	Likert	0,833	1,000	-0,410	-0,414	-0,263	-0.355
Pain relief	VAS	-0,346	-0,410	1,000	0,802	0,372	0,072
	Likert	-0,515	-0,414	0,802	1,000	0,367	0.156
Quality of life	VAS	-0,214	-0,263	0,372	0,367	1,000	0,430
	EQ-5D	-0.244	-0.355	0,072	0,156	0,430	1,000
Correlations between GPSq and isolated scales							
Pain intensity	VAS	0,911	0,754	-0,290	-0,447	-0,282	-0.363
	Likert	0,702	0,900	-0,313	-0,487	-0,401	-0.512
Pain relief	VAS	-0,294	-0,447	0,820	0,801	0,458	0.512
	Likert	-0,365	-0,284	0,756	0,833	0,542	0.424
Quality of life	VAS	-0,379	-0,350	0,176	0,159	0,886	0.419
	EQ-5D	-0,266	-0,355	0,152	0,156	0.464	0,978

VAS: Visual Analogue Scale; EQ-5D: EuroQol-5D

Pearson correlation measures the degree of linear relationship between two parametric variables (VAS) and assuming a normal distribution of the variables; and Spearman correlation between two non-parametric variables (Likert). Correlations between the same scales are written in grey background. The diverging average correlation (italics) is 0,38 and the convergent (bold) is 0.88.

Table 4: Correlation intra e inter-scales between GPSq and isolated scales.

3.6.4 Construct validity: GPSq could distinguish and detect significant differences between cases and control scores groups (Table 1) related to pain level and safety variables. Furthermore, correlations between the same traits (pain intensity and relief) but dissimilar methods showed the largest correlation with higher scores (0.8), except for the correlation between pain relief (VAS and Likert [0.521]) as it is supposed to be (Supplementary Material Table 3). As explained above, the highest correlation was evidenced between the same trait (pain intensity) and different methods (VAS [$r = 0.936$], Likert [$r = 0.833$]); and the lowest between different traits and methods ($r=0.190$). As we hypothesised, the second-largest correlation was found between the same method and different traits (Likert, mean 0.46; maximum 0.554); and lowest (mean 0.324) between different traits and methods. Discriminant validity was confirmed due to correlations with different traits, and the same or different methods (GPSq, VAS pain intensity and Likert pain relief [$r = 0.190$]).

3.6.5 Canonical-correlation analysis: Supplementary Material Figure 3 showed that the two sets of random variables were highly correlated as $\text{cor}(A1, B1) = 0.999$, and $\text{cor}(A2, B2) = 0.956$.

4. Discussion

GPSq demonstrated adequate validity and reliability indicators to be used with confidence in outpatient patients experiencing CNCP. Considering the need for an objective and precise measurement tool for revealing CNCP patients' statuses patients, this study provides a questionnaire that easily assesses pain condition thanks

to clear, simple language. Furthermore, a gender gap was found in pain patients' caregivers that highlights the need for support interventions taking gender-specific risk factors into account. Metric validity was confirmed through known groups' expected differences. Here, cases referred to higher pain intensity and more AEs than the control group, as it is usual in our polymedicated pain population [12, 31]. Surprisingly, a gender gap was found in the cases' companions. Our data showed that female middle-aged women were the predominant providers of informal care for family members. What's worse, when women are the patients (as of our 63% Pain Unit cases), their sisters or daughters took this role maintaining the implicit gender stereotypes. This can be due to the unequal distribution of responsibilities due to societal and cultural demands that persist on women [32] who experience a higher caregiver burden [33] with a high impact on their health [34] being at high risk of a wide spectrum of hidden morbidities [35, 36]. A tailored-made gender perspective research should be incorporated in pain management highlighting the need to analyse research results by gender [37].

4.1 Reliability and validity

Reliability shows the homogeneous nature of the questionnaire tested, indicating that individuals reported identical pain scores at both time intervals due to the high ICC results (VAS pain, relief, and quality of life, mean correlation $r>0.8$). What's more, high κ correlations showed that there was little difference between measurements (VAS, Likert). Also, an instrument for clinical decision-making is considered valid when Pearson or Spearman correlation

coefficients are high [38]. In the present study, all clinical variables evaluated had a coefficient correlation higher than $r=0.8$, almost perfect for the quality of life ($r=0.978$). Thus, our data also provide metric validity to the GPSq and confirm its convergent/discriminant validity. In addition, results showed a higher correlation with the rest of clinical variables (pain, quality of life) through a Likert evaluation than by a line at VAS to record pain. This increases the accuracy of our objective GPSq measure. Our questionnaire's content validity was performed in line with experts' criteria in CNCP management which constitutes the importance of its use-value and justification [39]. Consequently, our findings indicated that when used under the same conditions, as described in our methodology, clinicians could use the GPSq with confidence in terms of its validity. Furthermore, using integrated and self-reported GPSq instead of isolated scales could be more practical for the patient, since it only fills in a page with all the scales integrated, and also for the doctor who can interpret the questionnaire more clearly and quickly.

4.2 Limitations

The GPSq questionnaire consists of validated scales since it allows us to ascertain the patient's condition in several health areas in just one medical appointment. However, some limitations should be taken into account. Firstly, the total number of subjects studied was relatively small and this can compromise the ability to find differences. A minimum number was calculated using a "convenience sample" of patients attending the pain clinic. This may compromise valid statistical analysis.

Secondly, control patients were divided into two groups (cases' companions and patients from other units) due to the differences observed. This could place constraints in terms of an inappropriate choice of control group because the partners of the patients cannot be

completely independent controls. What's more, AEs may be due to pain treatment, or concomitant medical conditions. This could introduce a bias [36] mediated by several other variables (socio-demographic or cultural variables, or what's more, ethnicity) [32] which are more relevant than pain status. Finally, EQ-5D scale was used instead of SF12 -that provides a wide broad coverage of different health domains [40] in order to obtain the VAS quality of life score, an item comparable with others VAS records. In fact, we used the GPSq questionnaire in previous studies, in different pain population at our Pain Unit, with optimal results and low cost of resources [10, 11].

5. Conclusions

This study formally established that the GPSq shows good psychometric properties of reliability, validity, and responsiveness, enabling it to be used to measure CNCP in outpatient pain settings. Furthermore, a gender gap was demonstrated due to the difficult situation of female caregivers which should be recognized, devoting more effort to supporting their health.

Author Contributions

Jordi Barrachina, Javier Muriel, Cèsar Margarit, Beatriz Planelles, Pura Ballester, Thomas Zandonai, and Ana Maria Peiró were involved in the conception and design of the study. Jordi Barrachina, Javier Muriel, Miguel Richart, Domingo Morales, and Ana Maria Peiró were involved in the analysis and interpretation of the data. Jordi Barrachina, Javier Muriel, Miguel Richart, Martínez, Domingo Morales and Ana Maria Peiró designed the statistical analysis plan. Jordi Barrachina, Beatriz Planelles and Ana Maria Peiró wrote this manuscript. All authors were involved in drafting of the paper and revising it critically for intellectual content. All authors approved of the final version of this manuscript and agree to be accountable for all aspects of the work.

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Conflict of Interests

All authors declare there is no conflict of interests.

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Supplementary

Nombre y apellidos: _____ Género: _____
 Edad: _____ Peso (kg): _____ Fecha: ____/____/____

CUESTIONARIO DE ESTADO DE DOLOR

Global Pain State questionnaire (GPSq)

DOLOR	
Señale sobre la línea horizontal donde mejor se describa el dolor que siente <u>ahora</u>	MARQUE CON UNA CRUZ
	<input type="checkbox"/> 4 - Extremadamente intenso
	<input type="checkbox"/> 3 - Intenso
	<input type="checkbox"/> 2 - Moderado
	<input type="checkbox"/> 1 - Suave
	<input type="checkbox"/> 0 - Ninguno

ALIVIO	
Señale sobre la línea horizontal donde mejor se describa el alivio que siente <u>ahora</u>	MARQUE CON UNA CRUZ
	<input type="checkbox"/> 4 - Extremadamente aliviado
	<input type="checkbox"/> 3 - Intenso
	<input type="checkbox"/> 2 - Moderado
	<input type="checkbox"/> 1 - Suave
	<input type="checkbox"/> 0 - Ninguno

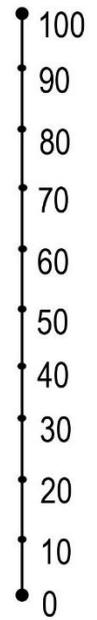
SÍNTOMAS DESDE LA ÚLTIMA CONSULTA			
<input type="checkbox"/> Somnolencia	<input type="checkbox"/> Impotencia sexual	<input type="checkbox"/> Boca seca	<input type="checkbox"/> Otros (indicar):
<input type="checkbox"/> Mareos	<input type="checkbox"/> Disminución deseo sexual	<input type="checkbox"/> Edema	
<input type="checkbox"/> Náuseas	<input type="checkbox"/> Cambio de peso	<input type="checkbox"/> Depresión	
<input type="checkbox"/> Vómitos	<input type="checkbox"/> Dolor de cabeza	<input type="checkbox"/> Insomnio	
<input type="checkbox"/> Estreñimiento	<input type="checkbox"/> Enrojecimiento piel	<input type="checkbox"/> Nerviosismo	
<input type="checkbox"/> Picor	<input type="checkbox"/> Piel seca	<input type="checkbox"/> Falta de apetito	

SI ESTOS SÍNTOMAS HAN MOTIVADO		
	Por su DOLOR	Por OTRAS causas
Ir a urgencias	<input type="checkbox"/> SÍ <input type="checkbox"/> NO	<input type="checkbox"/> SÍ <input type="checkbox"/> NO
Ingreso en el hospital	<input type="checkbox"/> SÍ <input type="checkbox"/> NO	<input type="checkbox"/> SÍ <input type="checkbox"/> NO
Cambio de medicación	<input type="checkbox"/> SÍ <input type="checkbox"/> NO	<input type="checkbox"/> SÍ <input type="checkbox"/> NO

Nombre y apellidos: _____ Fecha: ____/____/____

CUESTIONARIO DE ESTADO DE DOLOR

Global Pain State questionnaire (GPSq)

ESTADO DE SALUD Cuestionario de salud EQ-5D (European Quality of Life Scale)¹	
La respuesta de cada apartado que mejor describa su estado de salud en el día de <u>hoy</u> :	Señale sobre la línea vertical donde mejor se describa su estado de salud <u>hoy</u>
<p>Movilidad</p> <p><input type="checkbox"/> No tengo problemas para caminar</p> <p><input type="checkbox"/> Tengo algunos problemas para caminar</p> <p><input type="checkbox"/> Tengo que estar en la cama</p> <p>Cuidado personal</p> <p><input type="checkbox"/> No tengo problemas con el cuidado personal</p> <p><input type="checkbox"/> Tengo algunos problemas para lavarme o vestirme</p> <p><input type="checkbox"/> Soy incapaz de lavarme o vestirme</p> <p>Actividades cotidianas (p. ej. Trabajar, estudiar, hacer las tareas domesticas, actividades familiares o durante el tiempo libre)</p> <p><input type="checkbox"/> No tengo problemas para realizar mis actividades cotidianas</p> <p><input type="checkbox"/> Tengo algunos problemas para realizar mis actividades cotidianas</p> <p><input type="checkbox"/> Soy incapaz de realizar mis actividades cotidianas</p> <p>Dolor/malestar</p> <p><input type="checkbox"/> No tengo dolor ni malestar</p> <p><input type="checkbox"/> Tengo moderado dolor o malestar</p> <p><input type="checkbox"/> Tengo mucho dolor o malestar</p> <p>Ansiedad/depresión</p> <p><input type="checkbox"/> No estoy ansioso ni deprimido</p> <p><input type="checkbox"/> Estoy moderadamente ansioso o deprimido</p> <p><input type="checkbox"/> Estoy muy ansioso o deprimido</p> <p>Comparado con mi estado general de salud durante los últimos 12 meses, mi estado de salud de hoy es:</p> <p><input type="checkbox"/> Mejor</p> <p><input type="checkbox"/> Igual</p> <p><input type="checkbox"/> Peor</p>	<p>El mejor estado de salud imaginable</p>  <p>El peor estado de salud imaginable</p>

OCUPACIÓN ACTUAL: Trabajador en activo Parado Jubilado Ama de casa**INGRESOS ECONÓMICOS:** Menos de 500€ Entre 500-1000€ Más de 1000€

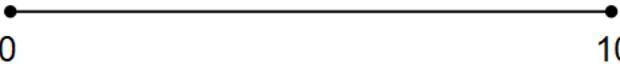
Muchas gracias por completarla, dásela al personal facultativo

¹ Validado por: Vartainen P, Mäntyselkä P, Heiskanen T, et al. Validation of EQ-5D and 15D in the assessment of health-related quality of life in chronic pain. *Pain*. 2017;158(8):1577-1585.

Name and surnames: _____ Gender: _____
 Age: _____ Weight (kg): _____ Date: ____/____/____

Global Pain State questionnaire (GPSq)

PAIN	
Point to the horizontal line where the pain you are feeling <u>now</u> is best described	MARK WITH A CROSS <input type="checkbox"/> 4 – Extremely severe <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 1 - Mild <input type="checkbox"/> 0 - None
	

RELIEF	
Point to the horizontal line where the relief you are feeling <u>now</u> is best described	MARK WITH A CROSS <input type="checkbox"/> 4 – Extremely relieved <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 1 - Mild <input type="checkbox"/> 0 - None
	

SYMPTOMS SINCE THE LAST CONSULTATION			
<input type="checkbox"/> Somnolence	<input type="checkbox"/> Sexual Impotence	<input type="checkbox"/> Dry mouth	<input type="checkbox"/> Others (indicate):
<input type="checkbox"/> Dizziness	<input type="checkbox"/> Decreased sexual desire	<input type="checkbox"/> Edema	
<input type="checkbox"/> Sickness	<input type="checkbox"/> Weight change	<input type="checkbox"/> Depression	
<input type="checkbox"/> Vomiting	<input type="checkbox"/> Headache	<input type="checkbox"/> Insomnia	
<input type="checkbox"/> Constipation	<input type="checkbox"/> Redness of the skin	<input type="checkbox"/> Nervousness	
<input type="checkbox"/> Itch	<input type="checkbox"/> Dry skin	<input type="checkbox"/> Lack of appetite	

IF THESE SYMPTOMS HAVE MOTIVATED		
	Because of your PAIN	Because of OTHER reasons
Go to emergency department	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO
Admission to hospital	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO
Change your treatment	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO

Name and surnames: _____ Date: ____/____/____

GLOBAL PAIN STATE questionnaire (GPSq)

HEALTH STATE EQ-5D Health questionnaire (European Quality of Life Scale)¹	
<p>By placing a tick in one box in each group below, please indicate which statements best describe your own health state today</p> <p>Mobility</p> <p><input type="checkbox"/> I have no problems in walking about</p> <p><input type="checkbox"/> I have some problems in walking about</p> <p><input type="checkbox"/> I am confined to bed</p> <p>Self-Care</p> <p><input type="checkbox"/> I have no problems with self-care</p> <p><input type="checkbox"/> I have some problems washing or dressing myself</p> <p><input type="checkbox"/> I am unable to wash or dress myself</p> <p>Usual activities (e.g. work, study, housework family or leisure activities)</p> <p><input type="checkbox"/> I have no problems with performing my usual activities</p> <p><input type="checkbox"/> I have some problems with performing my usual activities</p> <p><input type="checkbox"/> I am unable to perform my usual activities</p> <p>Pain/Discomfort</p> <p><input type="checkbox"/> I have no pain or discomfort</p> <p><input type="checkbox"/> I have moderate pain or discomfort</p> <p><input type="checkbox"/> I have extreme pain or discomfort</p> <p>Anxiety/Depression</p> <p><input type="checkbox"/> I am not anxious or depressed</p> <p><input type="checkbox"/> I am moderately anxious or depressed</p> <p><input type="checkbox"/> I am extremely anxious or depressed</p> <p>Compared to my general health state for the past 12 months, my health state today is:</p> <p><input type="checkbox"/> Better</p> <p><input type="checkbox"/> The same</p> <p><input type="checkbox"/> Worse</p>	<p>Draw a line to the vertical line to whichever point on the scale indicates how good or bad your health state is <u>today</u></p> <p style="text-align: center;">Best imaginable health state</p> <div style="text-align: center;"> </div> <p style="text-align: center;">Worst imaginable health state</p>

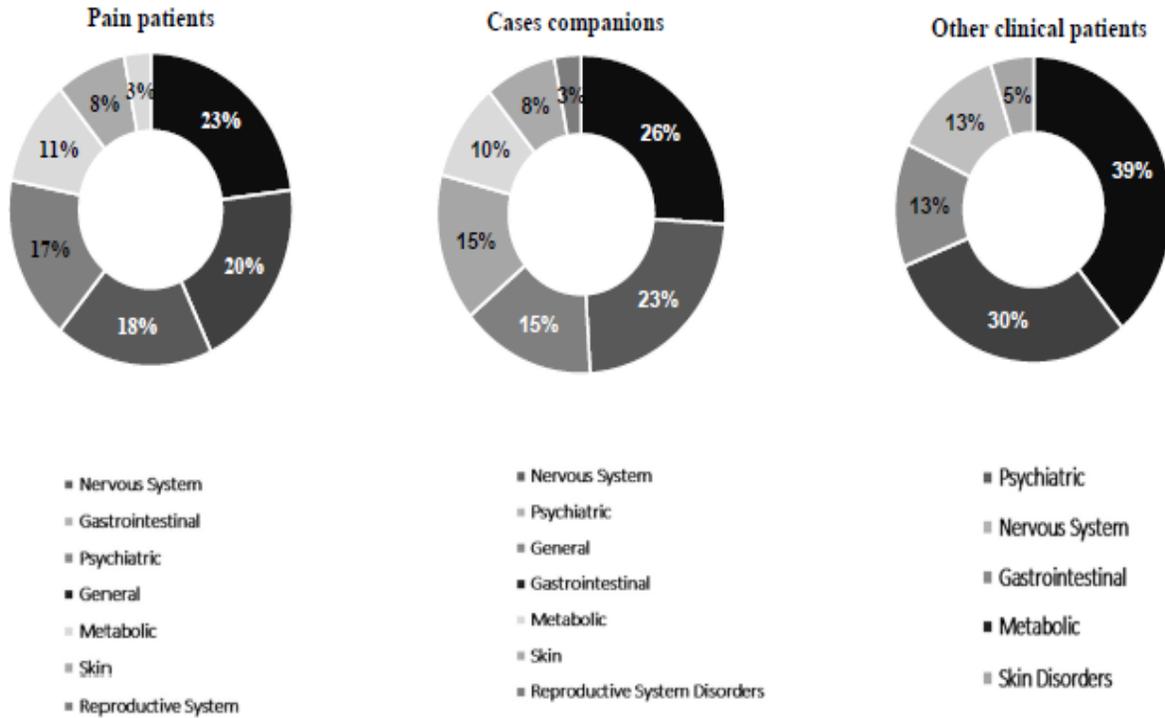
CURRENT OCUPATION: Active employment Unemployed Retired
 Homemaker

ECONOMIC INCOMES: Less than 500 € Between 500-1000 € More than 1000 €

Thank you very much for completing it, give it to the medical staff

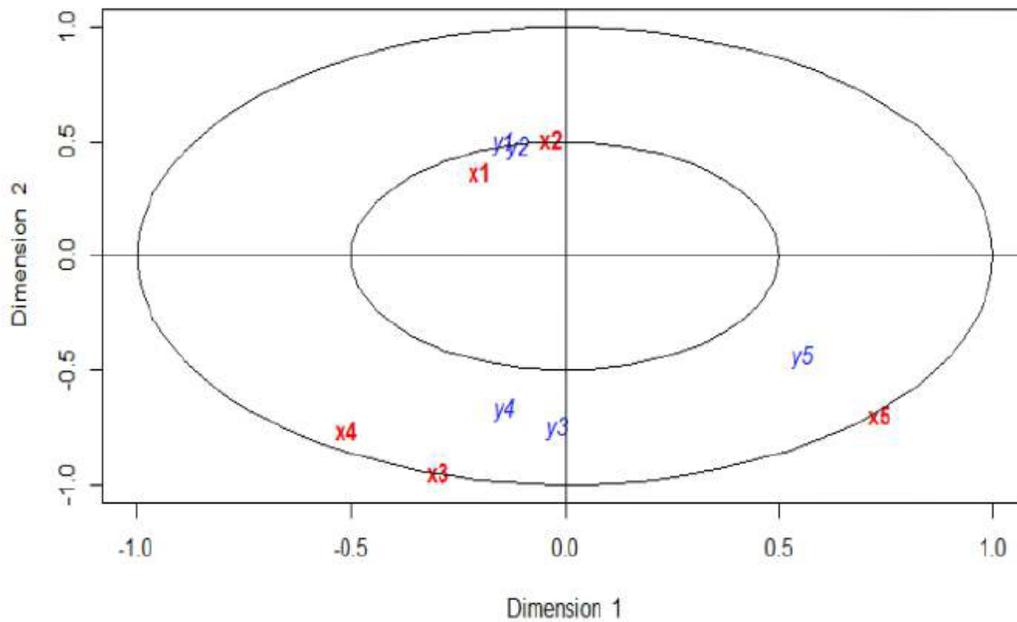
¹ Validated by: Vartainen P, Mäntyselkä P, Heiskanen T, et al. Validation of EQ-5D and 15D in the assessment of health-related quality of life in chronic pain. *Pain*. 2017;158(8):1577-1585.

Supplementary Figure 1: GPSq questionnaire, with the English version and the Spanish version, which was validated in this study.



Note: PU: Pain Unit Cases; PC: Control; CC: Other clinical’s units controls; AEs: Adverse Events.

Supplementary Figure 2: Adverse Events (AEs) frequency by system depending on the group. A) case group (PU), B) Patients’ companions’ group (PC), and C) Patients from other clinical Units (CC).



Supplementary Figure 3: Variables plotted on the first two canonical variates.

EQ-5D Dimensions		Case	Control	Control		P-Value
		PU (n=38)	PC and CC (n=52)	PC (n=27)	CC (n=25)	PU vs. PC + CC PC vs. CC PU vs. CC
Mobility, No. (%)	No problems to walk	6 (16%)	13 (36%)	6 (25%)	7 (58%)	.048 ¹
	Some problems to walk	32 (84%)	22 (61%)	18 (75%)	4 (33%)	.005 ²
	I must lay in bed	0 (0%)	1 (3%)	0 (0%)	1 (9%)	.0345 ³
Personal care, No. (%)	No problems	18 (47%)	18 (49%)	14 (56%)	4 (33%)	.9924 ¹
	Some problems	18 (47%)	17 (46%)	10 (40%)	7 (58%)	.781 ²
	Many problems	2 (6%)	2 (5%)	1 (4%)	1 (9%)	.4208 ³
Daily activities, No. (%)	No problems	11 (29%)	13 (36%)	9 (36%)	4 (36%)	.7590 ¹
	Some problems	20 (53%)	18 (50%)	12 (48%)	6 (54%)	.932 ²
	Many problems	7 (18%)	5 (14%)	4 (16%)	1 (10%)	.8486 ³
Pain, No. (%)	I have no pain	0 (0%)	7 (19%)	2 (8%)	5 (42%)	.0145 ¹
	Moderate pain	34 (89%)	25 (68%)	19 (76%)	6 (50%)	.0007 ²
	Much pain	4 (11%)	5 (13%)	4 (16%)	1 (8%)	.0493 ³
Anxiety/Depression (A/D), No. (%)	No A/D	12 (32%)	20 (51%)	15 (56%)	5 (42%)	.1655 ¹
	Moderately	23 (61%)	18 (46%)	11 (40%)	7 (58%)	.321 ²
	Very A/D	3 (7%)	1 (3%)	1 (4%)	0 (0%)	.5184 ³

P-value<0.05 is written in bold font, ¹PU patients vs PC + CC. ²PC vs CC. ³PU vs CC. Chi-square Test was carried out in all the statistical analyses.

Supplemental Table 1: Results of EuroQol-5D (EQ-5D) depending on the dimension affected at cases (PU, pain patients' group) and control group (PC, cases companions and n=CC, patients from other clinical units).

Variables	Cases (n=38)			Control PC (n=27)			Control CC (n=25)		
	Estimate	Standard Error	P-value	Estimate	Standard Error	P-value	Estimate	Standard Error	P-value
Pain intensity (VAS, 0-100 mm)	-0.318	0.268	0.249	0.503	0.2	0.241	-0.688	0.263	0.047
Quality of life (EQ-VAS, 0-100 mm)	0.047	0.032	0.161	0.047	0.023	0.29	0.088	0.032	0.042
Age (years)	0.027	0.065	0.683	-0.588	0.131	0.14	0.064	0.041	0.206
Sex (female, male)	1.356	1.3	0.308	1.499	1.188	0.427	1.109	1.072	0.348
AEs (number)	-0.042	0.294	0.163	-0.834	0.182	0.137	-0.119	0.516	0.826

*P value <0.05 is in bold font. VAS, Visual Analogue Scale (0-100mm); EQ- VAS EuroQol scale (0-100mm); AEs, Adverse Events.

Supplemental Table 2: Multiple linear regression of descriptive, clinical, and pharmacological parameters with Visual Analogue Scale (VAS) relief intensity scores for the Pain Unit (PU), Patients' companions (PC) and Clinical Units (CC) groups.

	Similar trait/dissimilar method	Similar method/dissimilar trait	Dissimilar trait/method
GPSq	0,936 ^a	0,527 ^c	0,190 ^e
	0,521 ^b	0,554 ^d	0,446 ^f
Isolated Scales	0,833 ^a	0,414 ^c	0,289 ^e
	0,802 ^b	0,346 ^d	0,372 ^f

Note: The matrix was performed to assess the relation between the different traits (pain intensity, relief intensity) and different methods (Visual Analogue Scale and Likert). ^a Pain intensity VAS and Likert; ^b Pain relief VAS and Likert; ^c VAS pain and relief; ^d Likert pain and relief; ^e VAS pain and Likert relief; ^f Likert pain and VAS relief

Supplemental Table 3: Convergent/discriminant validity for Global Pain Scale questionnaire (GPSq) and isolated scales and multitrait-multimethod matrix.



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