Article

A novel Multi-dimensional Clinical Response Index dedicated to improving global assessment of pain in patients with Persistent Spinal Pain Syndrome after spinal surgery, based on a real-life prospective multicentric study (PREDIBACK) and machine learning techniques

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Abstract: The multidimensionality of chronic pain forces us to look beyond isolated pain assessment such as pain intensity, which does not consider multiple key parameters, particularly in patients suffering from post-operative Persistent Spinal Pain Syndrome (PSPS-T2). Our ambition was to provide a novel Multi-dimensional Clinical Response Index (MCRI), including not only pain intensity but also functional capacity, anxiety-depression, quality of life and objective quantitative pain mapping assessments, the objective being to capture patient condition instantaneously, using machine learning techniques. Two hundred PSPS-T2 patients were enrolled in a real-life observational prospective PREDIBACK study with 12-month follow-up and received various treatments. From a multitude of questionnaires/scores, specific items were combined using exploratory factor analyses to create an optimally accurate MCRI; as a single composite index, using pairwise correlations between measurements, it appeared to better represent all pain dimensions than any other classical score. It appeared to be the best compromise among all existing indexes, showing the highest sensitivity/specificity related to Patient Global Impression of Change (PGIC). Novel composite indexes could help to refine pain assessment by changing the physician's perception of pa-

tient condition on the basis of objective and holistic metrics, and by providing new insights to therapy efficacy/patient outcome assessments, before ultimately being adapted to other pathologies.

Keywords: Composite score; Machine learning, PSPS, Failed Back Surgery Syndrome (FBSS); Chronic pain; Pain Intensity; Quality of Life; Pain Mapping; Pain Surface; Functional Capacity; Psychological Distress; Anxiety and Depression

1. Introduction

A substantial fraction of patients operated from spine (10-50%), [1] develop new or persistent back and/or leg pain postoperatively [2–5]. This pain entity, previously named Failed Back Surgery Syndrome, was recently classified as Persistent Spinal Pain Syndrome type 2 (PSPS-T2) [6,7]. Like other types of pain, PSPS-T2 is considered as an unpleasant sensory and emotional experience influenced by biological, psychological, and social factors, which leads to a decrease in health-related Quality of Life (QoL) [7–10]. PSPS-T2 constitutes a major public health issue and a considerable financial burden for society [11]. The heterogeneity of PSPS-T2 etiologies [12,13] and patient characteristics [14,15] make it difficult to identify with clarity which therapeutical option should be prioritized among many others, the objective being to obtain the best outcomes for our patients, according to their complex pathways.

Despite constant innovation in digital technology and Artificial Intelligence (AI), pain remains assessed by "gold-standard tools", such as the Numerical Pain Rating Scale (NRPS) score, from 0 (no pain) to 10 (the worst imaginable pain), [16]. These numeric scales massively influence daily pain practice (as an example, change in opioid prescription is traditionally based on NPRS≥4), they serve as reference cut-offs to recommend, or not, eligibility to therapies (as another example, a pain decrease ≥50% on VAS must be observed on a chronic refractory patient in order to consider a Spinal Cord Stimulation (SCS) trial successful and to permanently implant a patient with SCS [17,18]. Their main advantage is to be simple to use, but their major limitation is to fail to consider more than one of the several different dimensions of pain, such as functional disability [10,19–21] or psychological distress [2,10,22].

In addition, other limitations of unidimensional sporadic pain intensity assessment scales can be deplored, especially insofar as they cannot be quantitatively captured: positional changes, multifocal pain, mixed pain components [23,24], daily variability of pain depending on efforts, mechanical loads, pain typology, pain characterization, influence of psycho-social factors, impact on function, catalyzed by pain medication side effects, as many pieces of one complex puzzle, colonizing and then progressively devastating all dimensions of a chronic pain patient's life, as "black ink pervades a blotting paper sheet".

Moreover, in clinical daily practice, pain intensity, functional disability, psychological distress and quality of life assessments, when evaluated, are subjectively and independently considered, as opposed to clinical experience concluding in massive interlaying of these different, but permanently interconnected, pain dimensions.

Aiming to better understand PSPS-T2 patient profiles, mixture of mixed effect regression models have previously been used to determine the impact of pain intensity, functional disability, and psychological distress on health-related Quality of Life (QoL) perception [10]. This study showed that 2 different classes of PSPS-T2 patient can be identified: The first class corresponds to patients with QoL mainly affected by functional disability and psychological distress, whereas the second class corresponds to the patients with QoL mainly affected by pain intensity and psychological distress. All in all, this study showed, with robust evidence, that consideration of pain intensity change

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within time does not reflect the evolution of a chronic pain patient's QoL. As a mirror of the multidimensional concept of pain, a multidimensional composite score should reflect a holistic evaluation of the problem [25], and potentially provide a reliable standardized clinical assessment of therapy efficacy, in the context of a complex pathway.

In alignment with this approach, we introduced machine learning techniques to create a Multidimensional Clinical Response Index (MCRI), representing with high accuracy the related global health status of PSPS-T2 patients, in a real life observational prospective study. Our objectives were (i) to determine, by using pairwise correlations between measurements, if MCRI accuracy would reflect all/each of the pain dimensions, better than any other available pain score, as a single composite index and, (ii) to compare the sensitivity/specificity of each pain score vs MCRI, regarding the correlation with Patient Global Impression of Change (PGIC).

2. Materials and Methods

2.1. Study design

This prospective observational multicenter study, called PREDIBACK study, was designed to develop a new Multidimensional Clinical Response Index (MCRI). The study protocol was registered on Clinicaltrial.gov as NCT02964130 on November 15th, 2016. The study was approved by the ANSM (2016-A01144-47) as well as by the Ethics Committee West III and complied with the Declaration of Helsinki. Participants received explanations of the study and provided written informed consent before enrolment in this study.

2.2. Participants

2.2.1. Inclusion criteria

Recruitment of 200 PSPS-T2 patients was conducted in 5 French pain centers (Angoulême, Bressuire, La Rochelle, Niort and Poitiers) from January 2017 to Mars 2018. The eligibility of patients was identified through standard clinical practice at each site and all patients provided consent before enrolment. Patients had to be older than 17 years; had most recent back surgery more than 6 months ago; had to be suffering from persistent back and/or leg pain after spinal surgery for more than 6 months; had an average score of pain ≥ 4/10 using Numeric Pain Rating Scale (NPRS).

2.2.2. Non-inclusion criteria

Patient was or had been treated with spinal cord, subcutaneous or peripheral nerve stimulation, with an intrathecal drug delivery system; had already a confirmed PSPS-T2 diagnosis; had life expectancy of less than 12 months beyond study enrolment; Patient was unable to undergo study assessments or complete questionnaires independently; was a member of a vulnerable population; and/or investigator suspected substance abuse that might confound the study results.

2.3. Objectives

Our primary objective was to develop a Multidimensional Clinical Response Index (MCRI) able to reflect multidimensional pain assessment in a population of 200 patients presenting with PSPS-T2 and receiving various treatments during 12 months of follow-up. The secondary objectives were to determine (i) the correlation between MCRI and pain intensity score, quality of life, functional capacity score, anxiety/depression score, and pain mapping intensity changes, (ii) the comparative predictive power of detecting and reflecting clinical changes from the MCRI, pain intensity, quality of life, functional capacity, anxiety/depression and pain mappings, based on Patient Global Impression of Change (PGIC) at 3 (M3), 6 (M6), and 12 (M12) month follow-up.

2.4. The Multidimensional Clinical Response Index (MCRI)

2.4.1. Input data

In order to develop the MCRI, pain intensity, quality of life, functional capacity, anxiety/depression, pain mapping measurements were collected at baseline.

Pain intensity was measured with a Numerical Pain Rating Scale [26] (NPRS), ranging from 0 (no pain) to 10 (maximal pain that they could imagine). Clinical effectiveness was assessed through quality of life (EuroQol 5-Dimensions 5-Level questionnaire (EQ-5D-5L)) [27], functional disability (The Oswestry Disability Index questionnaire (ODI)) [28], anxiety/depression (The Hospital Anxiety and Depression Scale (HADS)) [29], Pain Mapping Intensity (PMI) changes (pain surface according to the pain intensity, PRISMap software) [30]. PRISMap provides accurate localization of the pain surface (in cm^2) associated with a coefficient related to pain intensity. Patients draw their pain surface directly on a tactile computerized interface in a predetermined body (individually adapted from the patient body mass index). A color code was used to determine pain intensity on the software: red=very intense, orange=intense, dark blue=moderate, light blue=mild [30]. Lower pain intensity was associated with coefficient 1, medium pain intensity with coefficient 2, intense pain intensity with coefficient 3, and very intense pain intensity with coefficient 4.

The equation was written as:

PMI=1*SurfaceLow+2*SurfaceMedium+3*SurfaceIntense+4*SurfaceVeryIntense.

Surface is the pain surface in cm^2, calculated by patented processing, associated with the intensity ranges from 1 to 4 where 1 is low pain, 2 is medium pain, 3 is intense pain and 4 is very intense pain.

2.4.2. Variable reduction and factor analysis

Correlation between items was determined using the repeated measure correlation coefficient. We calculated the Cronbach alphas at baseline for each questionnaire to assess the internal validity of the EQ-5D, ODI, HADS anxiety and depression subscales. The 29 Items from the 3 questionnaires (i.e. EQ-5D, ODI and HADS) were compiled in a single questionnaire. Global NPRS and PMI were kept as scores representing the "pain intensity" and "pain surface intensity" constructs.

2.4.3. Reduction of the number of items

A subset of items of each questionnaire (EQ-5D, ODI, HADS) was selected and used to determine the final dimensions of the MCRI.

First, clinically redundant items were deleted from the questionnaires, based on the construct they measured. Second, an Exploratory Factor Analysis (EFA) was conducted in order to remove items that had very low loadings (i.e. loading <0.3) in all the factors. We also removed items with very high loadings on the same factor. The idea was that such items were highly correlated, and hence provided redundant information. The item

with the higher loading between two redundant items was kept. The Kaiser-Meyer-Olkin measure of sampling adequacy was used to assess the suitability of our data for factor analysis. In the EFA step, the number of latent factors was determined using the Very Simple Structure (VSS) criterion, parallel analysis [31] and theoretical validity (the clinical relevance factor). For factor extraction, we used the principal axis factoring method. Promax rotation was used to provide correlated factors (called oblique solutions) since the different chronic pain dimensions (i.e. pain intensity and functional disability) were correlated.

We conducted a confirmatory factor analysis in order to test whether the factors obtained represented an underlying construct of the items they contained. To properly account for the clustered nature of the data (repeated measures longitudinal data) we used a two-level CFA (within-patient and between-patient effects). In CFA, model parameters were estimated using the maximum likelihood estimation method with robust (Huber-White) standard errors and a scaled test statistic [32] where all the variables were standardized to allow comparability. The model fit was tested using a Chi-squared test with Yuan-Bentler correction, since our variables did not have normal multivariate distribution (tested using the Henze-Zirkler's multivariate normality test). Goodness of fit was assessed using the Root Mean Square Error of Approximation (RMSEA) and the Comparative Fit Index (CFI). An RMSEA value under 0.05 indicates an excellent fit, and values between 0.05 and 0.08 indicate an acceptable fit. For CFI, a value between 0.90 and 0.95 is considered acceptable and a value of 0.95 or greater indicates an excellent fit.

EFA was conducted using the psych package while CFA was conducted using the lavaan package using the R software (Version 3.6.0; R Foundation for Statistical Computing; Vienna; Austria).

2.4.4. Final factor analysis and unidimensional assessment

The previously developed EFA results (Factors and their item loadings) were used in order to determine each factor score. Factor scores were extracted using the Bartlett approach [33].

Patients were described by each of the pain constructs represented by the scores extracted from the EFA plus pain intensity (NPRS score) and PMI. Each constructed score was standardized to a [0,100] interval to improve interpretability. The correlation at baseline of the scores was obtained and the standard pain evaluation measures (i.e. NPRS, ODI score, EQ-5D index, HADS total score and PMI) were determined using Spearman's rho and its 95% confidence interval.

2.4.5. Multidimensional assessment

Scores from different constructs were included in a Principal Component Analysis (PCA) in order to obtain a new assessment score summarizing the patient's pain state. The first component of the PCA was used as a summary score named MCRI. The MCRI was standardized to [0,100] to facilitate its interpretation. We also used PCA on the original scores of the questionnaires (i.e. ODI percentage, HADS total score, NRPS, EQ-5D index and PMI) in order to compare with the MCRI developed by EFA.

2.4.6. The correlation between MCRI and NPRS, EQ-5D, ODI, HADS and PMI

NRPS, ODI, EQ-5D, NPRS, HADS, and PMI were collected at 3, 6, 9 and 12 month-follow-up. The MCRI was then calculated for the M3, M6 and M12 follow-up period. The correlation between MCRI and the other parameters was calculated from M3 to M12 using Spearman rho coefficients.

2.4.7. Identifying the Patient Global Impression of Change (PGIC) using the MCRI, NPRS, EQ-5D, ODI, HADS and PMI

Patient satisfaction was assessed with Patient Global Impression of Change (PGIC). PGIC is a 7-point scale depicting a patient's rating of overall improvement from 0 (very much worse" to 7 (very much improved) (Fergusson & Scheman 2009). Self-perceived clinical improvement is considered satisfactory when the patient reports a PGIC score ≥ 6 and is considered unsatisfactory when the patient reports a PGIC score ≤ 5. The Area Under the ROC Curve (AUC) for detection of satisfactory self-perceived clinical improvement (PGIC score ≥ 6) was calculated using the change between baseline and at 3, 6, 9 and 12-month follow-up for all outcomes (MCRI, ODI, EQ-5D, NPRS, PMI and HADS). We also calculated the optimal cut-off points of the changes in the MCRI, NPRS, EQ-5D, ODI, HADS, and PMI based on the simultaneous maximization of specificity and sensitivity for detecting satisfactory self-perceived clinical improvement.

The relationship between PGIC and changes score was tested using the Jonckheere-Terpstra test, which Jonckheere-Terpstra test presupposes a tendency (increase or decrease) in the distribution location statistic between the ordinal variable groups. A p-value of less than 0.05 was considered as statistically significant.

Missing values were not imputed; and data were analyzed according to an available-case principle.

3. Results

3.1. Follow-up and missing data description

Out of the 200 included patients, 7 were removed of the analysis due to spine surgery (Flowchart available in Figure 1). Out of the remaining 193 patients, 186 (96.4%) completed questionnaires at baseline, 155 (80.3%) at 3-month, 150 (77.7%) at 6-month, 131 (67.9%) at 9- and 12-month follow-up.

3.2. Variable reduction and factor analysis

Due to their redundancy, 3 items were removed from the questionnaire: 2 items from the EQ-5D questionnaire (item-4 "Anxiety/Depression" and item-5 "Pain/Discomfort") and 1 item from the ODI (item-1 "Pain intensity").

3.2.1. First exploratory analysis

The first exploratory analysis was performed on the 26 remaining items using data from all time points. This initial EFA showed a 2-factor structure, which explained 22% of the total variance. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.87, indicating adequacy of the sample. The first factor consisted of 9 items over 10 from the ODI questionnaire, 3 items over 5 from the EQ-5D, and 1 item over 14 from the HAD. The second factor consisted in the remaining items of the HADS questionnaire (13 items), where 3 items had loadings < 0.3. These 3 items were consequently removed from the analysis.

3.2.2. Final exploratory analysis

A final exploratory factor analysis with 2 factors was performed on the remaining 23 items. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.87 indicating that a factor analysis is suitable for these 23 items. In a parallel analysis, we found that the eigenvalues from the current data were greater than eigenvalues of the simulated random data for 2 factors. The VSS criterion also supported the two-factor structure. The factor

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loadings obtained from this exploratory factor analysis and the correlations between these factors are presented in Table 1. Figure 2 presents the structure of the final 2-factor model and Table 1 the items in the functional disability (PA1) and depression/anxiety (PA2) factors.

Figure 1. Flowchart of study participants. EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; NPRS: Numeric Pain Rating Scale; HADS: Hospital Anxiety and Depression Scale; CSQ: Coping Strategies Questionnaire.

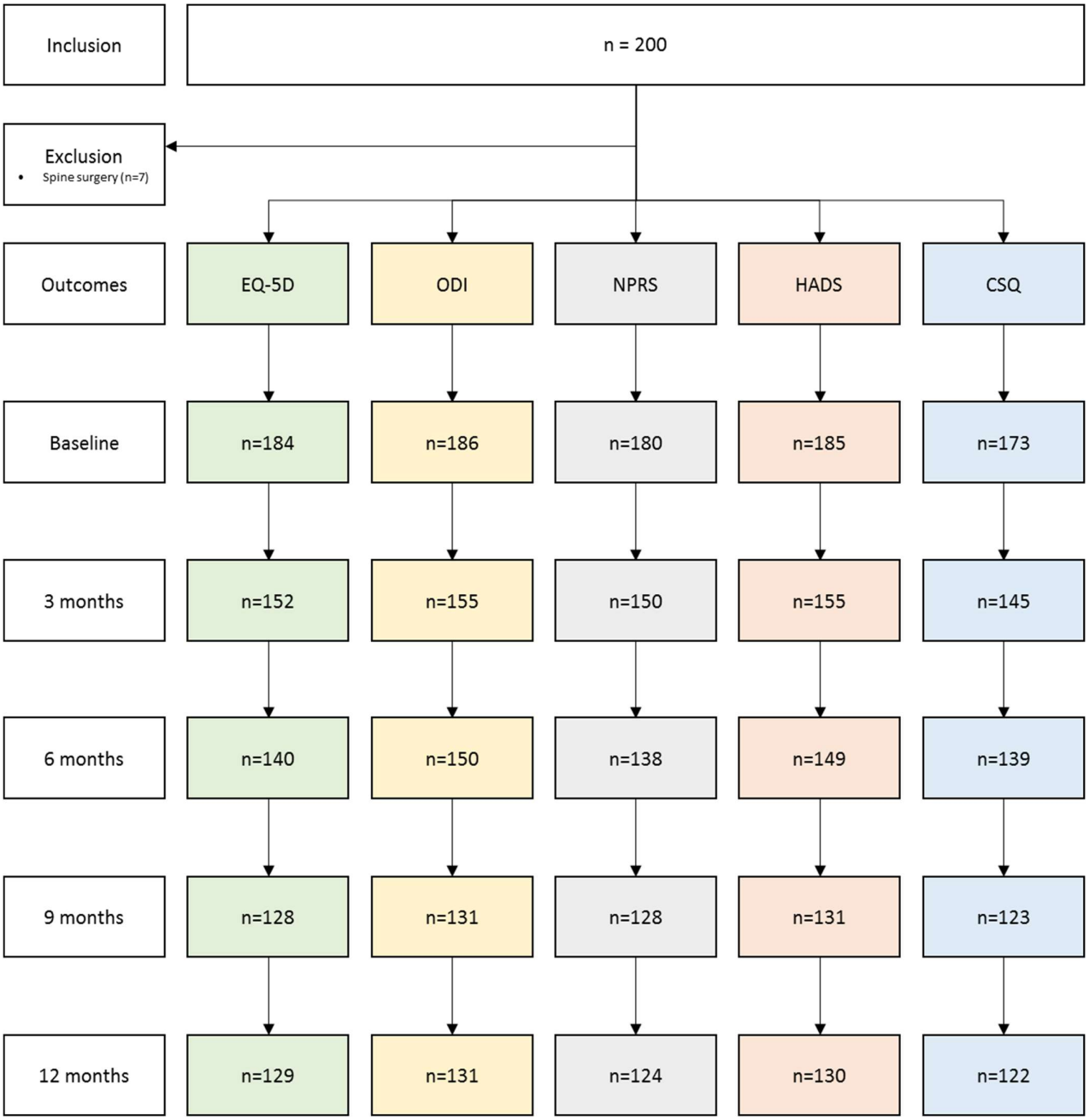

Table 1. Factor loadings and correlations between factors based on EFA.

Item	Functional Disability	Depression / Anxiety
EQ-5D_Mobility	**0.53**	0.05
EQ-5D_Self care	**0.48**	-0.07
EQ-5D_Usual activities	**0.48**	0.09
ODI_Personal care	**0.46**	0.03
ODI_Lifting	**0.31**	**-0.07**
ODI_Walking	**0.47**	-0.06
ODI_Sitting	**0.54**	-0.12
ODI_Standing	**0.59**	**-0.12**
ODI_Sleeping	**0.32**	0.11
ODI_Sex life	**0.40**	0.14
ODI_Social life	**0.34**	0.19
ODI_Travelling	**0.47**	0.05
HAD_Feeling tense or 'wound up'	0.11	**0.31**
HAD_Enjoying thing you used to enjoy	0.16	**0.43**
HAD_Feeling that something awful is about to happen	-0.10	**0.52**
HAD_Laughing and seeing the good side of things	0.04	**0.50**
HAD_Worrying thoughts going through your mind	-0.03	**0.51**
HAD_Feeling cheerful	0.05	**0.45**
HAD_Feeling slowed down	**0.30**	0.29
HAD_Frightened feeling like 'butterflies' in the stomach	-0.15	**0.70**
HAD_Looking forward with enjoyment to things	0.05	**0.49**
HAD_Sudden feeling of panic	-0.06	**0.56**
HAD_Enjoying a good book or radio/TV program	-0.09	**0.40**
Functional Disability	-	0.54

EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; HAD: Hospital Anxiety and Depression.

3.2.3. Confirmatory factor analysis and item selection

The results of the EFA described above with 23 items and 2 factors were used to construct our CFA model. Details of the standardized coefficients, 95% confidence intervals and p-values for within and between-patient effects of the CFA model are presented in Table 2. All coefficients were significant in their respective factors, except for the item “Enjoying a good book or radio/TV program” of the “depression & anxiety” factor.

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The goodness of fit model was not conclusive (Table 3). While the CFI of our model indicated poor fit (0.848 < 0.9), the RMSEA (0.046, CI90% = [0.042, 0.050] p-value (H0: RMSEA <= 0.05) = 0.9) indicated a good fit. The Chi-squared test with Yuan-Bentler correction was significant (p < 0.001), indicating poor fit.

The goodness of fit of each factor was examined using a one-factor CFA including only the items associated with the factor (Table 3). We found that the "depression/anxiety" factor had the lowest goodness of fit measures (CFI = 0.886; RMSEA = 0.064).

Figure 2. The EFA results with a promax rotation and principal axis factor extraction. PA1 is the factor associated with functional disability and PA2 is the factor associated with depression/anxiety (PA2). EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; HAD: Hospital Anxiety and Depression.

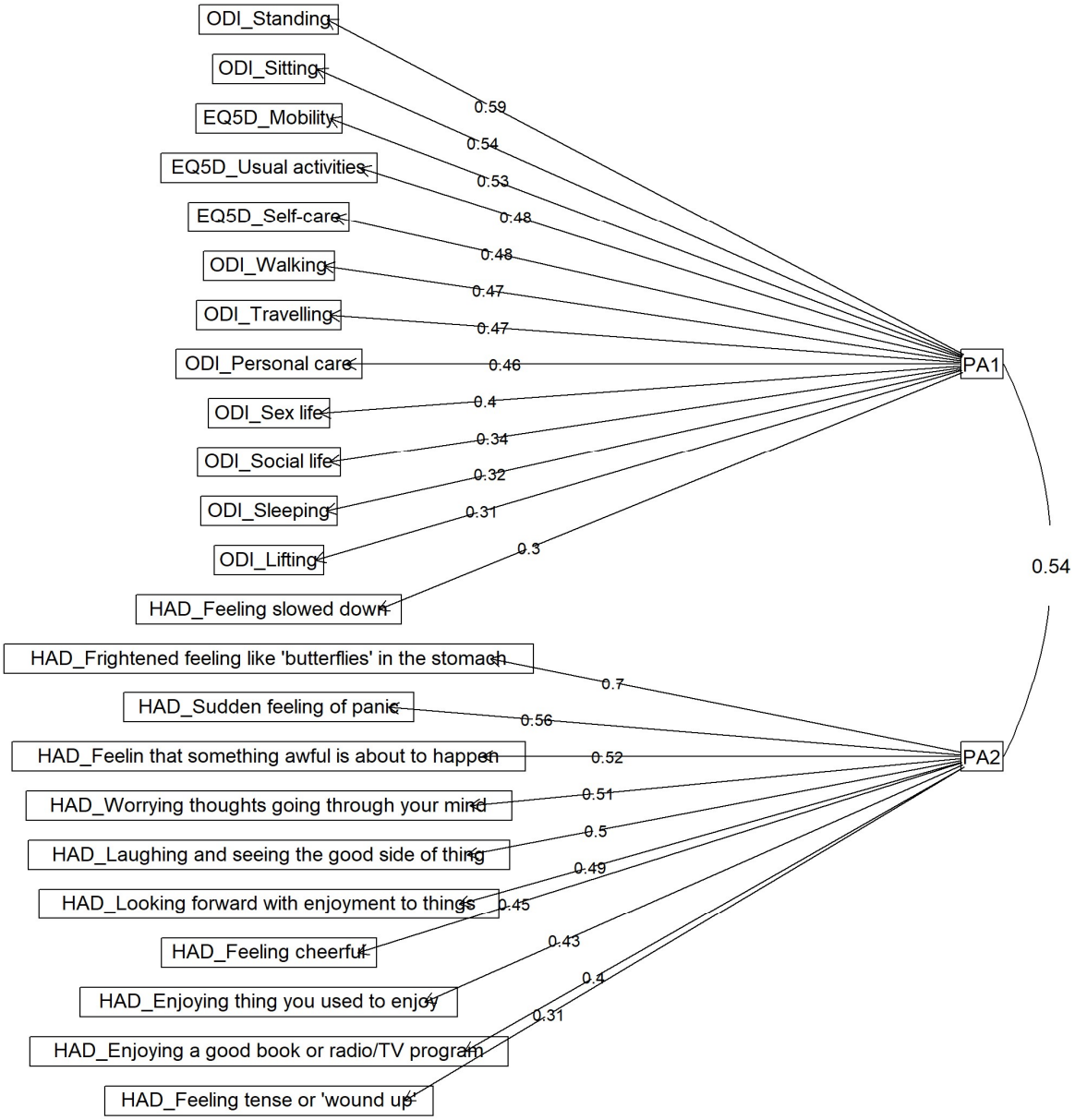

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Table 3. Goodness of fit measures for the CFA model obtained by including the 5 factors obtained from EFA and the CFA models including each factor and its associated items.

Goodness of fit measures	Two factor CFA model	Functional Disability	Depression & anxiety
Chi-squared test*	Chi2 = 940.66; p < 0.0001	Chi2 = 333.84; p < 0.0001	Chi2 = 260.00; p < 0.0001
RMSAE	0.046; CI90% = [0.042,0.050]	0.056; CI90% = [0.048,0.063]	0.064; CI90% = [0.056,0.072]
Robust CFI	0.848	0.876	0.886

** with the Yuan-Bentler correction*

3.2.4. Unidimensional assessment

The Bartlett method was used to extract each factor score from the final EFA. Figure 3 presents the distribution of the scores obtained from our EFA (scaled to [0,100]). Table 4 presents the correlations between the obtained scores and the ODI score, EQ-5D index, NPRS and HADS total score at baseline. More specifically, our results showed that the "depression & anxiety" factor was highly correlated with the HADS total score, although the number of items in this factor was smaller than the entire HADS questionnaire (10 over 14 items) (rho = 0.96; CI95% = [0.94,0.97]; p<0.0001). Similarly, the "functional disability" factor was highly correlated with the ODI score (rho = 0.92; CI95% = [0.89,0.94]; p<0.0001) and the EQ-5D index (rho = -0.81; CI95% = [-0.86,-0.74]; p<0.0001).

Figure 3. Violin plot of factor scores per visit of each construct. The lines represent the median and the first and third quartiles. The mean scores (/100) of each visit were also added to the plot. The violin plots show the distribution shape of the data at each visit. Wider sections of the violin plot represent higher probability that patients will have the given score; thinner sections represent a lower probability.

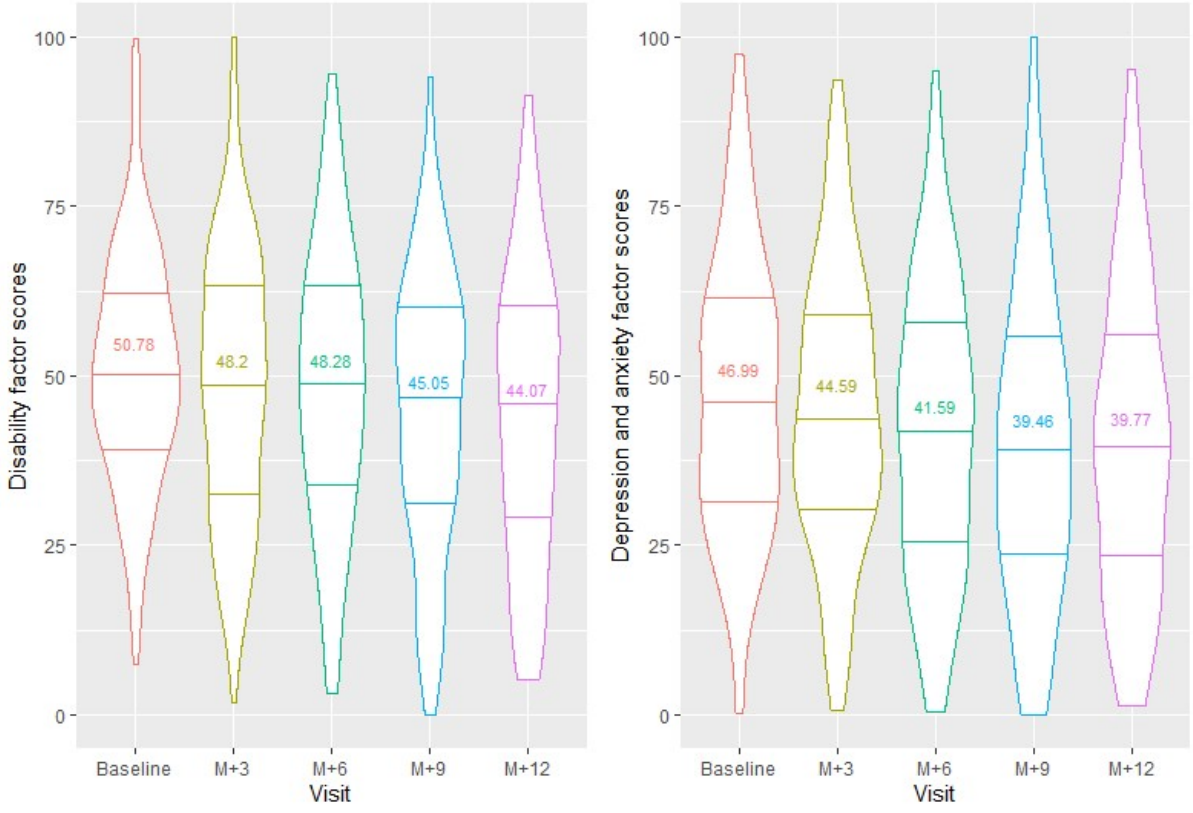

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Table 4. Correlations at baseline between the scores obtained from EFA and the standard pain evaluation measures.

	ODI score	EQ-5D index	NPRS	HADS total score	Mapping intensity
Baseline					
Functional Disability	0.92 CI95% = [0.89,0.94]	-0.81 CI95% = [-0.86,-0.74]	0.40 CI95% = [0.24,0.53]	0.35 CI95% = [0.20,0.49]	0.30 CI95% = [0.14,0.44]
Depression/Anxiety	0.38 CI95% = [0.23,0.52]	-0.49 CI95% = [-0.60,-0.35]	0.35 CI95% = [0.20,0.49]	0.96 CI95% = [0.94,0.97]	-0.02 CI95% = [-0.19,0.15]
M3					
Functional Disability	0.95 CI95% = [0.93,0.97]	-0.83 CI95% = [-0.88,-0.75]	0.52 CI95% = [0.36,0.65]	0.48 CI95% = [0.32,0.61]	0.30 CI95% = [0.12,0.47]
Depression/Anxiety	0.51 CI95% = [0.34,0.64]	-0.53 CI95% = [-0.65,-0.37]	0.36 CI95% = [0.18,0.52]	0.97 CI95% = [0.96,0.98]	0.04 CI95% = [-0.15,0.23]
M6					
Functional Disability	0.97 CI95% = [0.96,0.98]	-0.87 CI95% = [-0.91,-0.81]	0.68 CI95% = [0.55,0.78]	0.53 CI95% = [0.37,0.66]	0.26 CI95% = [0.07,0.43]
Depression/Anxiety	0.56 CI95% = [0.41,0.68]	-0.62 CI95% = [-0.73,-0.48]	0.48 CI95% = [0.31,0.62]	0.98 CI95% = [0.96,0.98]	0.11 CI95% = [-0.09,0.30]
M9					
Functional Disability	0.96 CI95% = [0.95,0.98]	-0.87 CI95% = [-0.91,-0.80]	0.60 CI95% = [0.44,0.72]	0.48 CI95% = [0.30,0.63]	0.36 CI95% = [0.16,0.53]
Depression/Anxiety	0.55 CI95% = [0.39,0.68]	-0.60 CI95% = [-0.71,-0.44]	0.41 CI95% = [0.21,0.57]	0.97 CI95% = [0.96,0.98]	0.24 CI95% = [0.03,0.43]
M12					
Functional Disability	0.96 CI95% = [0.95,0.98]	-0.86 CI95% = [-0.91,-0.79]	0.59 CI95% = [0.43,0.71]	0.57 CI95% = [0.40,0.70]	0.38 CI95% = [0.18,0.55]
Depression/Anxiety	0.54 CI95% = [0.38,0.68]	-0.52 CI95% = [-0.66,-0.35]	0.40 CI95% = [0.20,0.56]	0.92 CI95% = [0.88,0.95]	0.07 CI95% = [-0.15,0.28]

EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; NPRS: Numeric Pain Rating Scale; HADS: Hospital Anxiety and Depression Scale.

3.3. Multidimensional assessment

Principal Component Analysis (PCA) including the scores extracted from the EFA model, the NPRS scores and the PMI was used to determine the MCRI. The first principal component loadings, the percentage of explained variance and the first eigenvalue are presented in Table 5. The first component of the PCA explained 49.99% of the total variance. All variables had significant loadings in the PCA (>0.3). Loading was -0.811 for functional disability, -0.771 for NRPS, -0.684 for depression & anxiety score and -0.529 for PMI score.

We scaled the MCRI from 0 indicating the worst pain-related health status to 10 indicating the best pain-related health status.

Table 5: Composition of the first principal component.

Variables	1st principal component: 49.99% of the total variance
Eigenvalue	1.99
Functional Disability score	-0.811
NPRS score	-0.771
Depression & anxiety score	-0.684
Mapping intensity score	-0.529

NPRS: Numeric Pain Rating Scale.

3.4. The correlation between MCRI and NPRS, EQ-5D, ODI, HADS and PMI

The correlation between MCRI and the EQ-5D, ODI, NPRS, total HADS and PMI at baseline, and at 3, 6, 9 and 12-month follow-up are presented in Table 6.

The MCRI score was significantly correlated with the ODI score (rho = -0.677; CI95% = [-0.748,-0.591]; p-value < 0.0001), the EQ-5D score (rho = 0.690; CI95% = [0.606, 0.759]; p-value < 0.0001) and the NPRS score (rho = -0.677; CI95% = [-0.749,-0.589]; p-value < 0.0001) at baseline. The correlations of the MCRI with HADS score and PMI were moderate (HADS: rho = -0.622; CI95% = [-0.703,-0.525]; p-value < 0.0001; PMI: rho = -0.423; CI95% = [-0.533,-0.299]; p-value < 0.0001). The correlations at 3, 6, 9 and 12-month follow-up were also statistically significant and ranged from -0.527 to -0.828 (Table 6). All correlations were greater at 12-months than at baseline.

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Considering pairwise correlations between scores from EQ-5D, ODI, NRPS, HADS and PMI, we found that all the correlations were lower than those obtained with the MCRI.

Table 6. Correlation matrix of the MCRI, ODI score, EQ-5D index, total HADS score and mapping intensity at M0, M3, M6, M9 and M12 follow-ups.

Variables	MCRI	ODI	EQ-5D	NPRS	Total HADS	Mapping intensity
Correlations at baseline						
MCRI	1	-0.677***	0.690***	-0.677***	-0.622***	-0.423***
ODI	-	1	-0.631***	0.415***	0.279***	0.272***
EQ-5D	-	-	1	-0.346***	-0.434***	-0.250***
NPRS	-	-	-	1	0.289***	0.235**
Total HADS	-	-	-	-	1	0.131
Mapping intensity	-	-	-	-	-	1
Correlations at 3-month						
MCRI	1	-0.771***	0.714***	-0.761***	-0.616***	-0.527***
ODI	-	1	-0.728***	0.567***	0.472***	0.261***
EQ-5D	-	-	1	-0.521***	-0.492***	-0.244**
NPRS	-	-	-	1	0.406***	0.322***
Total HADS	-	-	-	-	1	0.050
Mapping intensity	-	-	-	-	-	1
Correlations at 6-month						
MCRI	1	-0.762***	0.788***	-0.828***	-0.631***	-0.537***
ODI	-	1	-0.776***	0.689***	0.542***	0.262***
EQ-5D	-	-	1	-0.659***	-0.586***	-0.310***
NPRS	-	-	-	1	0.442***	0.455***
Total HADS	-	-	-	-	1	0.106
Mapping intensity	-	-	-	-	-	1
Correlations at 9-month						
MCRI	1	-0.775***	0.803***	-0.774***	-0.655***	-0.637***
ODI	-	1	-0.784***	0.608***	0.611***	0.314***
EQ-5D	-	-	1	-0.645***	-0.581***	-0.350***
NPRS	-	-	-	1	0.483***	0.424***
Total HADS	-	-	-	-	1	0.244**
Mapping intensity	-	-	-	-	-	1
Correlations at 12-month						
MCRI	1	-0.758***	0.730***	-0.806***	-0.603***	-0.638***
ODI	-	1	-0.749***	0.514***	0.476***	0.456***
EQ-5D	-	-	1	-0.544***	-0.520***	-0.489***
NPRS	-	-	-	1	0.376***	0.553***
Total HADS	-	-	-	-	1	0.291***
Mapping intensity	-	-	-	-	-	1

* p<0.05; ** p<0.01; ***p<0.001. MCRI: Multidimensional Clinical Response Index; EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; NPRS: Numeric Pain Rating Scale; HADS: Hospital Anxiety and Depression.

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3.5. Identification of the Patient Global Impression of Change (PGIC) using the MCRI, NPRS, EQ-5D, ODI, HADS and PMI

Out of the 125 patients who reported their PGIC score at 12-months, 31 (24.8%) had satisfactory self-perceived clinical improvement (≥6) and 94 (75.2%) had unsatisfactory self-perceived change (≤ 5).

Table 7 presents the specificity and sensitivity of the change in the MCRI, ODI, EQ-5D, NPRS and total HADS to detect satisfactory and unsatisfactory self-perceived clinical improvement from the PGIC. The Jonckheere-Terpstra test showed a significant relationship between the change in the MCRI score and the PGIC from baseline to 12-month follow-up period ($p < 0.0001$). Likewise, the PGIC was also associated with the change in ODI, NPRS, EQ-5D, HADS and PMI scores ($p < 0.0001$).

The AUC showed that the changes in MCRI were the indicator most accurately identifying satisfactory self-perceived clinical improvement (AUC = 0.853) in comparison with the changes of the HADS total score (AUC=0.780), ODI score (AUC=0.737), NPRS (AUC=0.704), EQ-5D index (AUC=0.698) and PMI score (AUC=0.672).

Table 7. The specificity and sensitivity of MCRI, ODI, EQ-5D, NPRS, HADS and mapping intensity at detecting satisfaction of patients with their perceived change at each visit. Cut-offs that maximizes specificity and sensitivity were identified for each score in order to allow comparability.

	Satisfactory self-perceived clinical improvement	**Unsatisfactory self-perceived clinical improvement**
Change between M0-M3		
MCRI		
≥ 1.05	16 (sensitivity = 64.0%)	29
< 1.05	9	95 (specificity = 76.6%)
ODI		
≥ 6.7	14 (sensitivity = 56.0%)	27
< 6.7	11	93 (specificity = 77.5%)
EQ-5D		
≥ 0.13	12 (sensitivity = 50.0%)	38
< 0.13	12	79 (specificity = 67.5%)
NPRS		
≥ 2	13 (sensitivity = 52.0%)	25
< 2	12	88 (specificity = 77.9%)
HADS		
≥ 5	14 (sensitivity = 56.0%)	23
< 5	11	97 (specificity = 80.8%)
Mapping intensity		
≥ 468	15 (sensitivity = 60.0%)	44
< 468	10	77 (specificity = 63.6%)
Change between M0-M6		
MCRI		
≥ 1.05	19 (sensitivity = 65.5%)	25
< 1.05	10	90 (specificity = 78.3%)
ODI		
≥ 6.7	21 (sensitivity = 72.4%)	33
< 6.7	8	78 (specificity = 70.3%)
EQ-5D		
≥ 0.13	21 (sensitivity = 75.0%)	31
< 0.13	7	72 (specificity = 69.9%)

NPRS		
≥ 2	19 (sensitivity = 70.4%)	28
< 2	8	72 (specificity = 72.0%)
HADS		
≥ 5	17 (sensitivity = 58.6%)	21
< 5	12	90 (specificity = 81.1%)
Mapping intensity		
≥ 468	19 (sensitivity = 65.5%)	51
< 468	10	61 (specificity = 54.5%)
Change between M0-M9		
MCRI		
≥ 1.05	22 (sensitivity = 75.9%)	22
< 1.05	7	77 (specificity = 77.8%)
ODI		
≥ 6.7	19 (sensitivity = 65.5%)	27
< 6.7	10	71 (specificity = 72.4%)
EQ-5D		
≥ 0.13	16 (sensitivity = 57.1%)	30
< 0.13	12	65 (specificity = 68.4%)
NPRS		
≥ 2	20 (sensitivity = 69.0%)	33
< 2	9	60 (specificity = 64.5%)
HADS		
≥ 5	17 (sensitivity = 58.6%)	20
< 5	12	78 (specificity = 79.6%)
Mapping intensity		
≥ 468	12 (sensitivity = 55.6%)	37
< 468	15	57 (specificity = 60.6%)
Change between M0-M12		
MCRI		
≥ 1.05	24 (sensitivity = 77.4%)	19
< 1.05	7	75 (specificity = 79.8%)
ODI		
≥ 6.7	20 (sensitivity = 64.5%)	27
< 6.7	11	66 (specificity = 71.0%)
EQ-5D		
≥ 0.13	20 (sensitivity = 69.0%)	29
< 0.13	9	62 (specificity = 68.1%)
NPRS		
≥ 2	22 (sensitivity = 71.0%)	27
< 2	9	59 (specificity = 68.6%)
HADS		
≥ 5	20 (sensitivity = 64.5%)	22
< 5	11	71 (specificity = 76.3%)
Mapping intensity		
≥ 468	19 (sensitivity = 65.5%)	31
< 468	10	59 (specificity = 65.6%)

MCRI: Multidimensional Clinical Response Index; EQ-5D: EuroQol-5 Dimensions; ODI: Oswestry Disability Index; NPRS: Numeric Pain Rating Scale; HADS: Hospital Anxiety and Depression.

4. Discussion

Relying not only on pain intensity but also on quality of life, functional disability, anxiety/depression, and objective quantitative pain surface and intensity change assessments, we designed a multiplexed approach based on machine learning methods to capture the essence of pain with an alternative vision. This gave us the opportunity to develop a novel Multidimensional Clinical Response Index (MCRI), dedicated to improving global assessment in patients with Persistent Spinal Pain Syndrome after spinal surgery. Compared to other available index/scores, MCRI appears to be the most robust index when considering (i) pairwise correlations between each measurement and (ii) the sensitivity and specificity related to the patient global impression of change (PGIC). The findings of this study better define PSPS-T2 patient profiles with a global composite score and could be applied to analyze the therapeutic pathways of these patients.

4.1. The NRPS Score: a gold-standard tool, to assess patient pain and to conduct research in pain, but also a uni-dimensional subjective reflection of a complex puzzle. Past and Future considerations.

Nowadays, pain evaluation is systematically and primarily assessed with subjective tools such as the Numerical Pain Rating Scale (NRPS), Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Likert scale, etc. While necessary, these scales provide general and descriptive information that strongly limits accurate characterization needed to treat chronic neuropathic pain patients, especially those suffering from PSPS-T2. First, subjective scales have been demonstrated to be applicable to acute pain, at an instant "t", due to the difficulty of taking into account inter-individual variability and those occurring during the day. Secondly, these tools alone were not able to discriminate the mechanical and the neuropathic components of pain in an individual. In this context, PainDetect [34,35] and DN4 [36] questionnaires have been used in daily practice to bridge this gap, while scales are essentially dedicated to determining relative value of pain changes over time and/or per following a treatment application. In addition, one of the main limits is that while such tools provide global scores about a given individual, pain can affect a variable pain area or even be multifocal. Some previous studies used paper map drawings as a medium to determine the location of the pain (ref). However, they failed to offer objective measurements. In our study, pain localization was performed with patented processing encapsulated in a software (PRISMap), allowing to objectively quantify the pain surface changes in cm^2 [30]. In this way, patients suffering from pain localized at the upper or the lower limb extremities will not be impacted similarly on functional aspects. All in all, pain quantitative scale tools provide a good indication of pain intensity but are not able to provide a global picture of health-related quality of life of an individual, especially regarding pain.

As chronic pain involves multidimensional components, IMMPACT guidelines for pain assessment recommend including 1 or more measures of pain, as well as mean changes in physical and emotional functioning [37,38]. Based on these recommendations, we used 2 measures to assess pain (NRPS and PMI), 1 measure to assess physical function (ODI) and 1 measure to assess psychological component (HADS). Previous research focusing on the characterization of 163 patients suffering from PSPS-T2 showed that health-related quality of life was affected by several components [10]. Using a mixture model approach, the authors underscore that 2 classes of PSPS-T2 patients can be determined based on 3 dimensions: pain intensity, functional disability and psychological distress. The first 'pain intensity' class involved patients for whom health-related quality of life was more impacted by pain intensity and psychological distress, while the second 'functional disability' class involved patients for whom health-related quality of life was more impacted by functional disability and psychological distress. While psychological distress has been considered as systematically impacting health related quality of life,

one third of the PSPS-T2 patients were allocated in the 'pain intensity' class and two thirds in the 'functional disability class'. These findings reinforce the statement of Ballantyne and Sullivan [39,40], who claimed that pain intensity should not be systematically primarly targeted to achieve chronic pain relief. Taken together, these conclusions support the multidisciplinary approach provided by the biopsychosocial model [41,42].

4.2. PSPS-T2 Patient pathway. A ridgeline in the devastated landscape of pain for the physician. An Everest to climb for the patient.

Focusing on pain intensity or functional capacity would no longer see the forest for the trees. Put into social perspective, lower education level, lack of adaptive coping strategies and higher pain intensity were significantly associated with HRQoL and more impacted by pain perception [10]. By contrast, males who perceive their work as physical were more impacted by disability than pain intensity. Corroborating the latter findings, Naiditch et al. [9] reported that low Social Gradient of Health (SGH), concept used to describe the relationship between socioeconomic position and health, were overrepresented in PSPS-T2 patients (85.3%) in comparison with the general population (62.8%). PSPS-T2 patients with low SGH also presented the specificity of having significantly higher kinesiophobia, catastrophizing, and functional disability score than high SGH counterparts. Proposing the concept of Adapted Professional Activity in mirror of Adapted Physical Activity, another study reported that inactive patients were more likely to develop PSPS-T2 syndrome than active patients, especially when their profile was associated with low SGH [43]. The authors proposed a specific PSPS-T2 patient pathway, from initial clinical assessment including patient clustering and class analysis; followed by scrupulous identification of social factors that could guide the Multi-Disciplinary Team (MDT) through personal social-occupational-ergonomics coaching, the objective being to provide "Adapted Professional Activity" option [43].

The average length of the pathway leading to an initial MDT pain evaluation exceeds 12 years of evolution for post-op chronic refractory back and/or leg pain [44]. On the one hand, we might conclude that there is no emergency anymore to deploy various strategies for these patients; on the other hand, these devastated patients have less time than many others to try and eventually respond to an extreme diversity of available pain treatments, from pharmacotherapy to mesotherapy, from interventional procedures to neurostimulation techniques, from psychotherapy to re-surgery in carefully selected contexts. Given this complex pathway and the impossibility to compare, one by one, all the options that would provide the best outcomes for different subgroups of patients, the alternative solution would be to conduct large cohort prospective studies, where the primary endpoint would be not a VAS score decrease but rather a composite index, aiming to reflect global quality of life, regarding all pain dimensions. This would be the fertile substrate for further research perspectives based on the MCRI.

4.3. The need for a Polaroid picture of pain "in color", required to design a novel multi-dimensional composite pain assessment index.

Focusing on patient profiling, PSPS-T2 patients represent a vulnerable population, with limited capabilities of developing coping strategies and complex cognitive task elaboration process. They might benefit from a straightforward pain assessment, with reliable objective information, collected in a short amount of time, along their pathway, such as a MCRI composite index would be able to provide, rather than multiple independent questionnaires, inducing a loss of cooperation.

In a recent topical review, Gewandter et al. *[45]* indicated that the main potential advantage of composite outcome is that it helps to provide a more comprehensive assessment with respect to the complex world of pain. They highlighted the need to include clinical input with data from patients to ensure the clinical relevance of the composite score. Based on three different approaches, the author reported examples of published composite outcomes for pain. All the composite scores were built by combining cut-offs related to different scores [25]. For instance, Patel et al. [46] integrated input from NPRS and physical function (subscale of Short Form-36) to test 10 composite scores in 2287 patients for painful diabetic peripheral neuropathy and 1513 patients for postherpetic neuralgia, providing a composite score consisting of ≥ 50% improvement in pain or ≥ 20% improvement in pain combined with ≥ 30% improvement in physical function. Likewise, Pilitsis et al. [47], using data from 175 PSPS-T2 patients implanted with a spinal cord stimulation device, provided a composite score developed by an algorithm from pain intensity, catastrophizing, quality of life and physical capability so as to determine responders to spinal cord stimulation. The authors reported an average responder rate of 83.7% and 83.6% at 6- and 12-months. This responder algorithm was associated with high agreement with PGIC (96%). Even though our current composite MCRI has demonstrated lower sensitivity (77.4%) and specificity (79.8%), it might be hazardous to attempt to transpose the results obtained by Pilistsis et al. [47] to our practical approach, due to the difference of the therapy which was proposed to the patients (spinal cord stimulation vs real-life medical management in PREDIBACK). Furthermore, it appears that responder rates and correlations to PGIC were obtained with an algorithm, which had not been compared to other scores, making it difficult to put the results in perspective with ours. By using machine learning approach, we have accurately determined the load of each item, rather than each outcome, showing that MCRI was more sensitive and specific with regard to PGIC compared to all other outcomes (ODI, EQ-5D, NRPS, HADS, PMI). Furthermore, our study provides a Minimum Clinically Important Difference (MICD) of 1.05 points, which can detect pain changes with higher accuracy than other evaluation methods, through follow-up visits *[48]*. To give an idea: In pain studies a threshold of 30% or 2 points in VAS change *[37]* generally signals a significant difference between treatments. Here, with MICD of 1.05/10, thanks to this promising MCRI power of detection, we would exponentially increase the granularity of patient analysis and clustering.
In conclusion, it appears safe to assume that the MCRI score offers new perspectives to delineate comprehensive relevant clinical approaches for PSPS-T2 patients. However, we are aware that composite measurements should not be the exclusive way of assessing, by substitution to the individual domains of the composite outcome analysis; that said, that there is a real complementarity between the different ways of assessing, aimed at determining the optimal individual pathway for a specific patient.

4.4 A dynamic multiplexed vision of the patient pathway focusing on clinical outcomes, therapeutical strategy efficacy, patient profiling and AI-based outcome predictions.

Recently, Gewandter et al. [45] claimed that composite score can be used to incorporate relevant domains in primary conclusion to assess therapy efficacy. Echoing on that, MCRI would make it possible not only to assess therapeutical strategy efficacy with more objective and robust metrics throughout complex pathways, but ultimately to provide a quantitative substrate to further medico-economical extrapolations and AI-based predictive medicine, which will delineate the future of our indications, reimbursments, and optimized care by personnalizing the therapy.

4.5. Study strengths and limitations

In the general context of PSPS-T2 pain management, although our study is the first to develop a composite score of pain assessment, using a machine learning approach and through a prospective real-life study, there are substantial limitations which need to be addressed.

First, our current MCRI is specifically dedicated to PSPS-T2 patients and cannot be directly adapted to other pathologies or used to assess all therapy effects. This first step constitutes a strong baseline for future studies but clinical validations on cohorts would be useful to initiate a second phase, aimed at stratifying therapeutical choices and at rationalizing patient pathways.

Secondly, we have "only" used 5 dimensions to design the MCRI and we must admit that enriching MCRI by incorporating other dimensions might reinforce the robustness of our model, such as social component or Quality of Sleep. However, too many assessments might also decrease individuals' willingness to respond adequately to each questionnaire in clinical practice. This could constitute a barrier to enrolment and follow-up, especially in the context of research, potentially compromising the quality of the collected source information. MCRI potential users will have to agree on the most acceptable compromise to shape this index to vulnerable patients.

5. Conclusions

Because pain is a physical sensation which integrates psychological and functional dimensions, its assessment justifies the use of multi-dimensional tools, such as composite indexes. Applying Application of machine learning algorithms to pain intensity, pain surface, functional disability, psychological distress, and quality of life, led us to develop a novel Multidimensional Clinical Response Index (MCRI) allowing to determine a composite pain score to assess PSPS-T2 patients with high accuracy. MCRI appeared to be the best compromise among all existing indexes, also showing the highest sensitivity/specificity related to Patient Global Impression of Change (PGIC). This approach can be considered as the starting point to develop further models to evaluate therapy effects, in a prospective manner, using robust tools.

Author Contributions: The Trial Steering Committee consisting of P.R. and M.R. designed the study, approved the analysis plan, provided study oversight and contributed to interpretation of the data; B.L., M.M. (Many), K.N., N.N. and S.B. conducted the study and reviewed and approved the final article; M.B., A.O. and P.R. drafted the initial article with input and critical review from N.N., R.D., L.G., N.G. N.A., R.R. and M.M. (Moens); Statistical analysis was performed by A.O., P.Y.L. and Y.S.; M.B., A.O., P.Y.L. and Y.S. provided tables and designed the figures. All authors have read and agreed to the published version of the manuscript.

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