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Complex regional pain syndrome evolution is determined by both biological and psychosocial factors: a 1-year prospective observational study

Marc-Henri Louis[a,b,*], Valéry Legrain[a,c,d], Vladimir Aron[a], Lieve Filbrich[a,e], André Mouraux[a], Séverine Henrard[f,g], Laurent Guillaume[h], Dominique Mouraux[i,j], Olivier Barbier[k], Xavier Libouton[k], Anne Berquin[a,b]

Abstract

Complex regional pain syndrome (CRPS) is a challenging condition with unpredictable clinical evolution. Identifying early prognostic factors could transform patient management and improve outcomes. This prospective study followed 113 patients with early CRPS (<6 months) over 1 year to assess clinical evolution and investigate key predictors of chronification. Participants underwent repeated clinical assessments, quantitative sensory testing, and self-reported evaluations at 4 time points over 1 year. Multivariable mixed-effect models were used to identify independent early prognostic factors. Despite some improvement, 35% of the participants still met Budapest criteria at 1 year, with persistent pain, disability, and impaired quality of life. Sensory profiles appeared to stabilize after a few months, while body perception disturbance scores did not change during the follow-up period. Psychosocial factors, such as baseline disability, psychosocial severity, and social support, as well as body mass index and allodynia, were predictors of long-term outcomes. Biopsychosocial Early CRPS profiles defined through a latent class analysis carried out on the basis of data measured at inclusion revealed distinct clinical trajectories and showed stronger prognostic value than previously suggested CRPS classifications (eg, based on skin temperature). These findings highlight the importance of an early assessment incorporating biopsychosocial elements to stratify risk and tailor interventions. Our study paves the way for the development of a clinical tool to predict CRPS evolution, potentially enabling tailored treatments. Future research should validate these predictive models and explore their integration into routine practice, potentially improving the management of early CRPS.

Keywords: Complex regional pain syndrome, Prognosis, Prognostic factors, Biopsychosocial, Early, Chronification

1. Introduction

Complex regional pain syndrome (CRPS) is an important cause of chronic pain and disability but remains a poorly understood condition,[22] despite recent interesting findings.[19] However, its prognosis is still debated.

Early CRPS describes a stage of the condition that is potentially easier to manage and more likely to improve than *persistent CRPS*.[22] However, no clear consensus exists regarding the exact time point distinguishing these 2 stages, with proposed cut-offs typically ranging between 12 and 18 months after symptom onset.[22] As a result, the term early CRPS is often applied to a broad and somewhat imprecise timeframe. Whereas older research suggested a favourable evolution of early CRPS, with a majority of patients experiencing spontaneous recovery,[67] more recent prospective studies and systematic reviews showed rare complete remissions and a poor rate of return to work (RtW).[6,34] Some data show similar outcomes at 1 and 8 years, suggesting the absence of resolution after 12 months.[13] All these elements highlight the importance of investigating early factors influencing the evolution and therefore the risk of CRPS chronification. Yet, this topic remains largely unexplored as shown in a recent systematic review[42] where only 6 studies were found, most of which were considered at a high risk of bias. Among the identified potential predictors, 6 were supported by moderate evidence:

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[a] Institute of Neuroscience (IONS), Université Catholique de Louvain, Brussels, Belgium, [b] Department of Physical and Rehabilitation Medicine, Saint-Luc University Hospital, Brussels, Belgium, [c] Psychological Sciences Research Institute, Université Catholique de Louvain, Louvain-la-Neuve, Belgium, [d] Louvain Bionics, Université Catholique de Louvain, Louvain-la-Neuve, Belgium, [e] Health Psychology, Faculty of Psychology and Educational Sciences, Katholieke Universiteit Leuven, Leuven, Belgium, [f] Clinical Pharmacy and Pharmacoepidemiology Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium, [g] Institute of Health and Society (IRSS), Université Catholique de Louvain, Brussels, Belgium, [h] Clinique Saint Luc, ASBL Santé et Prévoyance, Namur, Belgium, [i] Department of Physical Therapy and Rehabilitation, Erasmus University Hospital, Université Libre de Bruxelles, Brussels, Belgium, [j] Laboratory of Applied Biology, Research Unit in Applied Neurophysiology (LABNeuro), Université Libre de Bruxelles, Brussels, Belgium, [k] Department of Orthopaedic Surgery, Saint-Luc University Hospital, Brussels, Belgium

**Corresponding author. Address. Ave Mounier 53, Boîte COSY B1.53.04, 1200, Brussels, Belgium. Tel.: +32 2 764 54 89. E-mail address: marc-henri.louis@uclouvain.be (M.-H. Louis).*

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anxiety, pain, disability, pain-related fear of movement, sex, and physical intensity of the triggering event.

The literature on CRPS prognosis originally considered biological factors,[11,63] such as skin temperature and sensory disturbances, as predictors. By contrast, psychological factors (commonly called *yellow flags*) have come to the fore more recently[4] as in many other pain conditions such as low back pain or adhesive capsulitis.[27,45,47] The identification of these factors in musculoskeletal disorders has led to the development of short questionnaires, allowing clinicians to quickly assess the prognosis of early conditions.[30,39] Furthermore, some of these tools were designed with the aim of adapting the therapeutic management and improving outcomes, with varying degrees of success.[31,32] A similar approach in CRPS has never been tried, probably because of the lack of established prognostic factors. Importantly, no prospective study has simultaneously included biological, psychological, and social factors. In addition, we recently identified 4 profiles of patients with early CRPS characterized by distinct clinical features and outcomes,[41] suggesting the existence of multiple pathophysiological mechanisms associated with different clinical trajectories. Their relevance and value in a longitudinal setting have not been assessed yet.

The purposes of this study were (1) to assess the clinical evolution of early CRPS (defined in this study as <6 months) during the 12 months following the onset and (2) to investigate potential early prognostic factors covering the span of the biopsychosocial model, potentially leading to the development of a tool allowing clinicians to predict patients' prognosis.

2. Methods

This observational longitudinal study followed the STROBE guidelines.[15] The protocol was approved by the local ethics committee (2022/28FEV/093) and was prospectively registered on ClinicalTrials.gov (NCT05337501). This study corresponds to the follow-up data of an early CRPS cohort (N = 113) previously published.[41]

2.1. Participants

The inclusion procedure was extensively described in Ref. 41. Participants were referred from 28 French-speaking Belgian clinical centres, contacted by phone (MHL), and then included from May 2022 to December 2023, the last follow-up being performed in December 2024.

Inclusion criteria were (1) over 18 years old, (2) meeting the Budapest clinical diagnostic criteria,[24] (3) symptoms onset from less than 6 months, (4) CRPS type I or II,[22] and (5) ability to understand and voluntarily sign an informed consent. Exclusion criteria were (1) insufficient French language skills to answer questionnaires, (2) personal previous history of CRPS at the same limb, (3) post-stroke CRPS type I (*shoulder-hand syndrome*), and (4) severe psychiatric or neurological disorders that would interfere with the participants' ability to complete the study tasks.

2.2. Procedures

Most participants were assessed 4 times in total, at inclusion and during 3 other sessions, respectively, at 4.5, 6, and 12 months following the onset of the condition, except for participants included after 4.5 months of condition duration who were assessed 3 times only (**Fig. 1**). Each assessment session lasted approximately 2 hours and involved identical procedures, including collection of demographic and clinical data, quantitative sensory testing,[54] and a visuospatial perception task (Temporal Order Judgement task[20]). To reduce the risk of bias, the testing room and the investigator (MHL) were identical for each participant. The subjects received financial compensation for their participation (€25 for each session). If a participant was unable to attend, a phone interview was conducted, and it was proposed that the participant complete the survey at home.

The day after each experimental session, the participant was invited to complete a set of questionnaires at home. The participant was informed that the questionnaires should preferably be completed in 1 session.

2.3. Measures

The collected data were extensively described in a previous study.[41] In brief, it included (1) demographical data (age, sex, body mass index [BMI], limb dominance, participant-reported comorbidities and related treatments, addictions, education level), (2) work-related variables (professional status, work type,[66] medico-legal conflict, work injury), (3) CRPS history (family or personal history of CRPS, physical intensity of the triggering event,[3] potential immobilization type and duration, CRPS duration at inclusion, ie, from the beginning of the symptoms and from the initial event, bone scan results), (4) CRPS clinical variables (localization, and spreading,[22] research Budapest criteria,[25] CRPS severity score [CSS],[25] neuropathic signs,[22] vasomotor signs, sudomotor signs, trophic signs, motor signs, current treatment), (5) revised-Bath-Complex Regional Pain Syndrome-Body Perception Disturbance Scale (r-B-CRPS-BPDS),[58] (6) Quantitative Sensory Testing (QST),[46,53] (7) Temporal Order Judgement (TOJ) task (point of subjective simultaneity [PSS] and slope[20]).

After each session, participants completed several questionnaires at home to assess functional, psychological, and social variables: (1) disability (QuickDASH for upper extremity,[7] Lower Extremity Functional Scale [LEFS] for lower extremity[28]), (2) quality of life (QoL) (EuroQol-5 dimensions—5 levels [EQ-5D-5L] [10]), (3) pain severity and interference (Brief Pain Inventory-short form [BPI-SF][36]), (4) pain-related fear of movement (Tampa Scale of Kinesiophobia-11 [TSK-11][64]), (5) anxiety and depressive disorders (Hospital Anxiety and Depression Scale [HADS][65]), (6) psychosocial factors associated with chronification of common musculoskeletal pain, labelled in this study *psychosocial severity* (French version of the Örebro Musculoskeletal Pain Screening Questionnaire-short form [ÖMPSQ-SF][49]), (8) pain coping strategies (Coping Strategies Questionnaire-French version [CSQ][33]), (7) perceived social support (Social Support Questionnaire-short form [SSQ6][50]), and (9) "general" pain sensitivity (Pain Sensitivity Questionnaire [PSQ][16]).

We also categorized patients using profiles determined in our previous study[41] using a latent class analysis (LCA[57]) based on 5 baseline characteristics: physical intensity of the triggering event, pressure pain threshold (PPT), r-B-CRPS-BPDS, presence of allodynia (sign), and ÖMPSQ-SF score. These parameters were chosen to reflect potentially relevant pathophysiological mechanisms of CRPS. The analysis yielded 4 *Biopsychosocial Early CRPS (BE-CRPS) profiles*, labelled based on their initial characteristics*: Mild CRPS*, *Moderate CRPS*, *Body representation disturbance [BRD] CRPS* and *Pressure allodynia CRPS* (n = 85). While *Mild* and *Moderate CRPS* differed mainly in baseline outcomes (poorer for *Moderate CRPS* than for *Mild CRPS*), *BRD* and *Pressure allodynia CRPS* showed the worst clinical profiles, distinguishing across all 5 LCA variables (**Fig. 2**, see Ref. 41 for details).

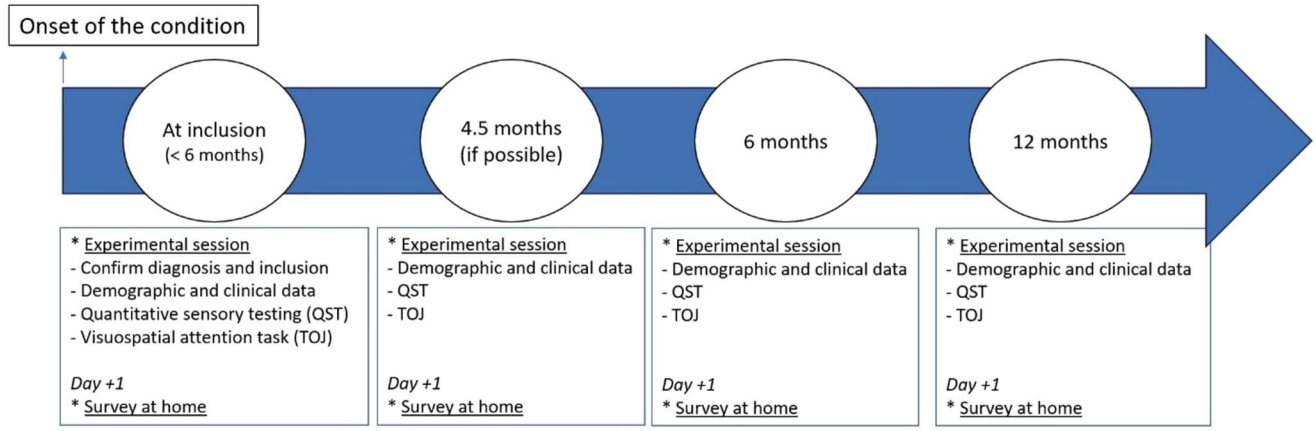

Figure 1. Study design.

2.4. Outcomes

The outcome parameters were selected to assess the 3 components of the International Classification of Functioning, Disability and Health (ICF)[37]: *body function and structure* (CSS, Budapest clinical criteria, pain intensity), *activity* (pain interference, disability), and *participation* (QoL and RtW). As per the aim of the ICF, the primary outcome was defined as the disability score. Return to work outcome was only assessed among participants working prior to CRPS onset (n = 77).

The outcomes were prospectively chosen, except for meeting the Budapest clinical criteria, which were added after the onset of this study, as it was thought to be a relevant add-on to CSS.

2.5. Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the Saint-Luc University Hospital. Statistical analyses were conducted using IBM SPSS Statistics 28 and R software (R × 64 version 4.2.3). A $P < 0.05$

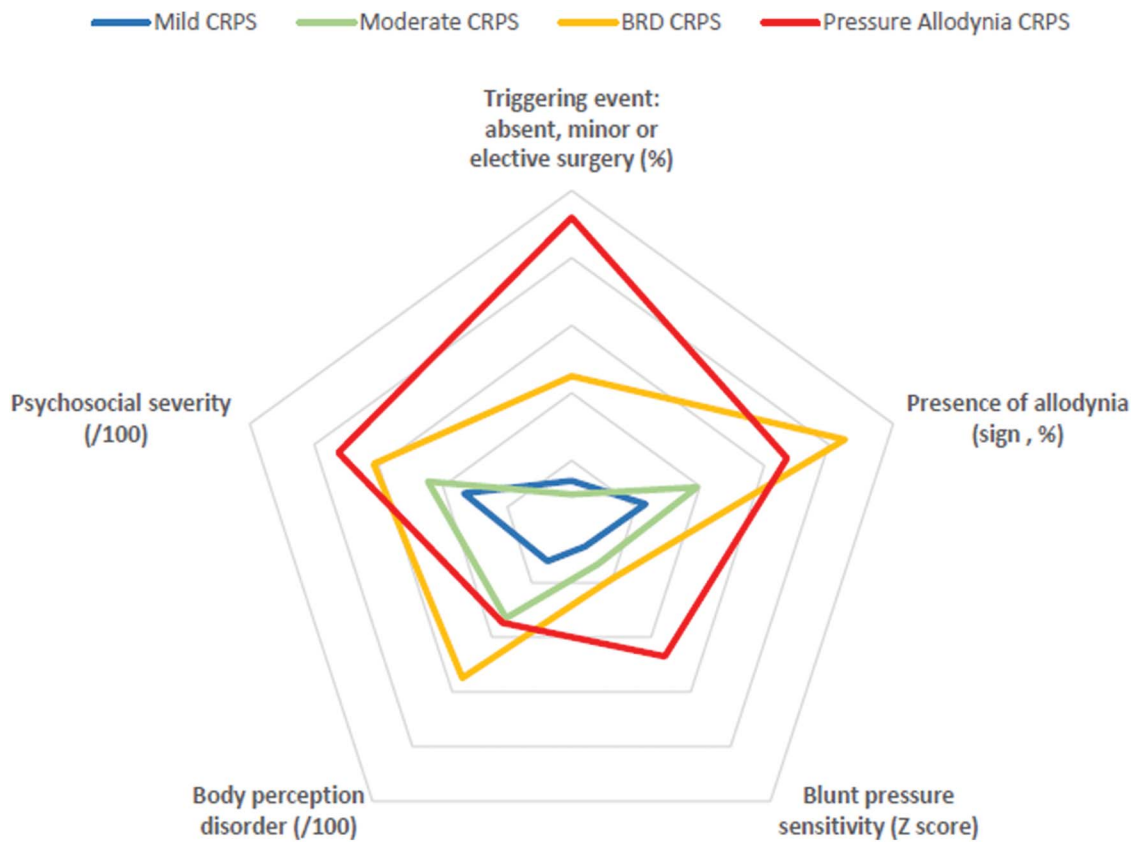

Figure 2. Variables entered in the latent class analysis, presented on a 0 (centre) to 100 scale for each profile (expressed by a mean or proportion). Triggering events were dichotomized between absent/minor trauma/elective surgery vs fracture/major trauma requiring surgical repair. The presence of allodynia (sign, any stimulus) is expressed as a rate within each profile. ÖMPSQ-SF score was used to indicate the psychosocial severity, mean pressure pain threshold (Z score, contralateral values normalized by the norms) was multiplied by 10, while body perception disorder corresponds to the mean r-bath-CRPS-BPDS normalized on a/100 scale (original score multiplied by 2.13). Abbreviations: LCA, latent class analysis; ÖMPSQ-SF, Orebro Musculoskeletal Pain Questionnaire—short form; r-B-CRPS-BPDS, revised-Bath-Complex Regional Pain Syndrome-Body Perception Disturbance Scale.

was considered statistically significant. The script used to analyse QST results is available at: https://github.com/vladaron/CRPS_longitudinal.

Characteristics of the participants were presented using mean and standard deviation (SD) for continuous variables, frequency, and percentages for categorical variables. The computation methods of the variables are detailed in the appendix (see supplemental digital content, http://links.lww.com/PAIN/C392).

TOJ task data were excluded from statistical analyses when parameters of the psychometric function could not be reliably estimated during the 40 trials of at least 1 of the 2 blocks, suggesting that the participant's performance was too inconsistent or below chance level (see supplementary section, 3. TOJ procedure, supplemental digital content, http://links.lww.com/PAIN/C392). Accordingly, data from 9 sessions were discarded (inclusion: 5/78; 4.5 months: 1/50; 6 months: 2/69; 1 year: 1/72). Threshold values were recoded so that the measure of perceptual simultaneity was expressed relative to the affected limb vs contralateral limb (rather than left vs right limb); positive values indicate a perceptual bias to the advantage of visual stimuli presented on the side of the affected limb, negative values to the contralateral limb. Potential systematic bias towards the affected or the contralateral side was investigated by comparing mean PSS values to 0 using a 1-sample *t* test.

We assessed the homogeneity of our sample by investigating significant differences between participants who completed only the home survey and the other participants (all variables at the inclusion, and outcomes at the last follow-up). Continuous variables were compared between these 2 groups using a Student *t* test or a Mann–Whitney *U* test according to their distribution, and the results were examined with histograms and normal QQ plots. Proportions of categorical variables were compared with a Pearson Chi-squared test. The same statistical tests were used to explore potential differences between the participants who still met the Budapest clinical criteria and the others at the last follow-up. Correlations were assessed using the Pearson coefficient.

Differences between time points were assessed using linear mixed models (LMMs) or generalized LMMs (random intercept for participants, no random slope), depending on the dependent variable (discrete or categorial). For prognostic models, we imputed the missing values (see below). As the aim of this study was to assess the role of early prognostic factors, only the baseline value of the predictors was included in those models. An example is provided in the supplementary data section (5. Example of participants' characteristics used in the prognostic models, supplemental digital content, http://links.lww.com/PAIN/C392).

2.5.1. Missing data management for prognostic models

We used a multiple imputation to replace the missing values[38,52] (considered as *missing at random*, ie, the likelihood of being missing is consistent within groups determined by the observed data) of each predictor at inclusion. Hence, 75 datasets were created using the mice R package,[12] and the imputed values were used to compute predictive multivariable models, pooled in a single output.

2.5.2. Building prognostic models

Included variables were selected based on a backward elimination procedure. It was performed with mice for logistic regression and with the mitml R package[23] for LMMs, as mice does not currently provide such an approach for these models. A complete explanation of the statistical method is available in the supplementary section (4. Explanation of the building prognostic models method, supplemental digital content, http://links.lww.com/PAIN/C392).

3. Results

Figure 3 shows the study flowchart. In total, we contacted 158 patients. Eventually, 113 participants performed the inclusion session, while 107 were assessed at the 1-year follow-up (drop-out rate: 5%). The participants were referred by general practitioners (12%, 5 centres), orthopaedists (50%, 9 centres), and physical medicine doctors (38%, 14 centres). During this study, some assessments were only performed remotely (**Fig. 2**). Consequently, some data were only collected for part of the cohort: clinical assessment, QST, and TOJ procedure. Participants who were assessed remotely did not significantly differ from the rest of the cohort in terms of demographic or clinical data at the inclusion or in terms of outcomes at 1 year ($P > 0.05$; *data not shown*).

3.1. Participants characteristics

3.1.1. Demographical inclusion variables

An extensive description and analysis of the demographic and inclusion characteristics of the participants is available in Ref. 41. They are briefly summarized in **Table 1**.

3.1.2. Clinical evolution

Table 2 shows the CRPS features of the cohort at each assessment. At 1 year, approximately 40% of the participants still described constant pain. The most prevalent features were motor changes (85%), while only 22% still reported sweating asymmetry or trophic changes. Regarding the clinical presentation, sweating was rarely observed (4%). However, weakness or reduction of RoM was still found in 75% of the cohort at 12 months. Concerning body perception, participants still presenting an *active* state (ie, meeting clinical Budapest criteria) reported similar disturbances to the early condition (ie, mean of the whole cohort at inclusion) or to persistent CRPS[58] (see supplementary section, 6. Supplemental digital content, Table S1, http://links.lww.com/PAIN/C392). We did not observe any influence of time on individual r-B-CRPS-BPDS score for participants still meeting the Budapest clinical criteria at 1 year (*effect of the time as a predictor in a univariate LMM: $P > 0.05$, data not shown*). For the whole cohort, time had a significant effect only at early stages (*effect of time as a predictor in a univariate LMM: $P < 0.05$; post hoc Bonferroni correction: $P < 0.05$ only between inclusion and 6-12 months assessments, data not shown*). The few participants (n = 11) who underwent surgery of the affected limb during follow-up showed similar outcomes to the other patients (*Chi-squared and independent t test, data not shown*).

Table 3 shows the biopsychosocial variables from the self-completed questionnaires at each time point (excluding outcomes, presented in the following section). Most variables improved over time (*effect of the time in univariate LMMs: $P < 0.05$*).

For the sake of completeness, comparisons between patients still meeting Budapest clinical criteria at 1 year with other patients for CRPS features and self-reported variables are available in the

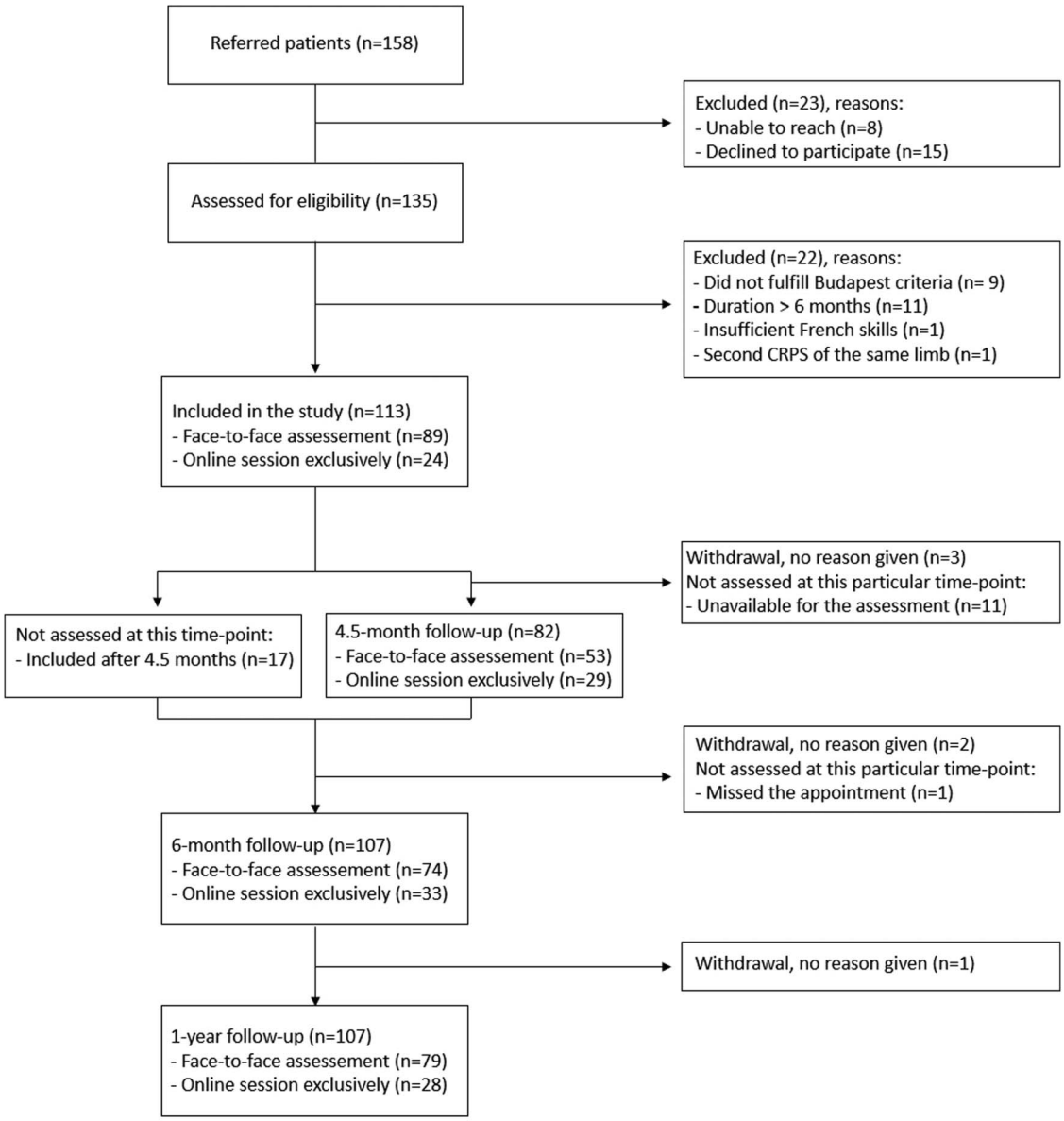

Figure 3. Flowchart of the study. Note: The number of participants assessed at 6 and 12 months is identical despite 1 more participant being lost to follow-up at 12 months, due to the inclusion of another participant who was not assessed at the 6-month time point.

supplementary section (6. Supplementary tables, supplemental digital content, http://links.lww.com/PAIN/C392).

3.1.3. Quantitative sensory testing results through 1 year

The sensory profile was fully assessed in 274 sessions (inclusion: n = 80; 4.5 months: n = 51; 6 months: n = 69; 12 months: n = 74). For logistical reasons, it was only possible to collect part of the QST data for some other sessions (n = 15).

Figure 4 summarizes the sensory profiles of participants at each time point. **Table 4** presents the normalized QST values by modality, and the potential effect of time, side, and their interaction on the different QST variables. For the sake of brevity, results from 4.5 months of follow-up were not presented in the tables and figures (but included in the LMMs). The raw values of each time point are also available in the appendix, with the number of participants for each assessment and modality.

Globally, participants, in comparison to normative data from healthy subjects,[43] were characterized by increased sensitivity to thermal painful stimuli (cold pain threshold and heat pain threshold) and blunt pressure (PPT), as well as a reduced sensitivity to nonpainful thermal stimuli (cold detection threshold [CDT], warm detection threshold [WDT], and thermal sensory limen [TSL]) and to some mechanical stimuli (MPS, mechanical detection threshold [MDT], and vibration detection threshold [VDT]).

The LMMs results showed that thermal pain thresholds, MDT, DMA, and WUR were stable over the 1-year period. Conversely, time significantly influenced the individual values of CDT, WDT, TSL, MPT, MPS, VDT, and PPT. In post hoc analyses, we only observed a significant difference between the inclusion values and some other time points, mostly at 1-year follow-up (at 4.5 months: CDT, TSL; at 6 months: CDT, MPT, MPS, PPT; at 12 months: CDT, WDT, TSL, MPT, MPS, VDT, and PPT). No difference between any other time points was found.

Regarding the effect of side (CRPS limb vs contralateral limb), most of the QST modalities differed significantly between the

Table 1

Baseline characteristics of participants.

Variables	n (%) or mean ± SD (*n* = 113)
Sex (women)	87 (77.0)
Age (y)	52.9 ± 13.3
BMI (kg/m^2)	26.2 ± 4.9
Smoking	
Currently	24 (21.2)
Pack-year	8.5 ± 14.3
Alcohol (units per week)	3.0 ± 7.2
Education level (y)	7.8 ± 2.8
History of CRPS	
Only personal	13 (11.5)
Only family	13 (11.5)
Both	1 (0.9)
Working before CRPS	77 (68.1)
Work type	
Not applicable	28 (24.8)
Minimal physical demands (mentally demanding work)	23 (20.4)
Mixed physically and mentally demanding work	23 (20.4)
Light physically demanding work	33 (29.2)
Heavy physically demanding work	6 (5.3)
Professional status at inclusion	
Workers	19 (16.8)
Medical part-time	5 (4.4)
Pensioner	23 (20.4)
Unemployed	5 (4.4)
Student	2 (1.8)
Sickness—invalids' beneficiary	59 (52.2)
Work injury	15 (13.3)
Medico-legal conflict with the employer or insurance company	15 (13.3)
Specialization of physician referring participant	
Orthopaedic	57 (50.4)
Physical medicine	43 (38.1)
General practice	13 (11.5)
Participant-reported comorbidities (previously to CRPS onset)	
Chronic pain	18 (15.9)
Anxiety	5 (4.4)
Depression	3 (2.7)
Insomnia	5 (4.4)
Asthma	4 (3.5)
Migraine	
With aura	6 (5.3)
Without aura	4 (3.5)
Diabetes	
Type I	2 (1.8)
Type II	3 (2.7)
Inflammatory diseases	0 (0)
Localization	
UE	67 (59.3)
Elbow	1 (0.9)
Hand/wrist	63 (55.8)
Only fingers	3 (2.6)
LE	46 (40.7)
Knee	3 (2.7)
Foot/ankle	43 (38.0)
Triggering event	
Minor incident/no known tissue injury	1 (0.9)
Soft tissue injury	15 (13.3)
Elective surgery	26 (23.0)
Fracture not requiring surgical repair	34 (30.0)
Major injury requiring surgical repair	37 (32.7)
CRPS duration (d)	75.8 ± 44.1
Duration since triggering event (d)	120.0 ± 51.1
Strict immobilization	
None	15 (13.3)
Cast	76 (67.3)
Only splint	22 (19.5)
Duration (wk)	4.7 ± 3.0
Median (min to max)	5 (0-15)
CRPS type II	11 (9.7)
Early CRPS profile*	
Mild CRPS	22 (25.9)
Moderate CRPS	31 (36.5)
Body representation disturbance CRPS	20 (23.5)
Pressure allodynia CRPS	12 (14.1)
Scintigraphy (n = 56)	
Positive	48 (85.7)
No argument for CRPS	8 (14.3)
Uptake ratio (affected/contralateral) (n = 48)	1.74 ± 0.53

* Based on Louis M-H et al. European Journal of Pain (London, England) vol. 29,2 (2025): e4785. doi:10.1002/ejp.4785.

CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; BMI, body mass index; UE, upper extremity; LE, lower extremity.

affected and the contralateral limb, regardless of the time point (exceptions: HPT, MDT, and WUR).

Finally, only PPT and DMA (presence vs absence of abnormal value) were significantly impacted by a different effect of time depending on side. In pairwise comparisons, we observed a significant difference between the PPT values at inclusion and the 3 other time points for the affected side (reduction of the gain of function), but no significant difference for the contralateral side. Similarly, we observed different rates of abnormal DMA between the inclusion and 4.5 months, but not for the control side.

3.1.4. Temporal order judgment task

As in our inclusion data,[41] we did not observe any systematic bias in visuospatial perception (whole cohort, upper or lower limb groups) for any of the follow-up time points (*P > 0.05, data not shown*). At follow-ups, none of the early CRPS profiles exhibited significant bias (*P > 0.05, data not shown*). Furthermore, we did not find any significant correlation between the computed PSS values and the r-Bath-CRPS-BPDS score for any time point. Eventually, the individual TOJ scores were stable at follow-up (*effect of time as a factor in a univariate LMM: P > 0.05, data not shown*).

3.2. Complex regional pain syndrome outcomes at 12 months

Table 5 and **Figure 5** summarize the evolution of each outcome (except for RtW, see below). It should be noted that participants included during the 3 months following CRPS onset did not report different outcomes at any follow-ups than those included between 3 and 6 months (*independent t test without correction: P > 0.05; data not shown*). A comparison of outcomes according

Table 2

Clinical evolution of CRPS.

Variables	n (%) or mean ± SD			
	Inclusion ($n = 113$)	4.5 mo ($n = 64$)	6 mo ($n = 86$)	1 y ($n = 105$)
Fulfill Budapest research criteria	89 (78.8)	25 (39.1)	38 (44.2)	25 (23.8)
CRPS symptoms				
Continuing pain	113 (100.0)	39 (60.9)	49 (57.0)	41 (39.0)
Hyperalgesia or allodynia	95 (84.1)	41 (64.1)	50 (58.1)	53 (50.5)
Temperature asymmetry	94 (83.2)	39 (60.9)	48 (55.8)	41 (39.0)
Skin color asymmetry	102 (90.3)	45 (70.3)	56 (65.1)	40 (38.1)
Sweating asymmetry	41 (36.3)	18 (28.1)	22 (25.6)	23 (21.9)
Swelling asymmetry	112 (99.1)	55 (84.6)	68 (79.1)	65 (61.9)
Trophic disturbances	62 (54.9)	30 (46.9)	22 (25.6)	26 (24.8)
Motor disturbances	113 (100.0)	59 (92.2)	83 (96.5)	89 (84.8)
Variables	**n (%) or mean ± SD**			
	Inclusion ($n = 89$)	**4.5 mo ($n = 53$)**	**6 mo ($n = 74$)**	**1 y ($n = 79$)**
Sensory signs				
Hyperalgesia to pinprick	54 (60.7)	19 (35.8)	34 (45.9)	24 (30.4)
Allodynia (any type)	42 (47.2)	11 (20.8)	16 (21.6)	17 (21.5)
Allodynia to light touch	14 (15.7)	5 (9.4)	6 (8.1)	9 (11.4)
Allodynia to pressure	26 (29.2)	5 (9.4)	11 (14.9)	15 (19.0)
Allodynia to cold	8 (9.0)	2 (3.8)	4 (5.4)	9 (11.4)
Allodynia to joint mobilization	15 (16.9)	3 (5.7)	5 (6.8)	7 (8.9)
Tactile hypoesthesia	10 (11.2)	4 (7.5)	7 (9.5)	10 (12.7)
None	20 (22.5)	29 (54.7)	34 (31.5)	46 (58.2)
Temperature sign				
Normal	49 (55.1)	33 (62.3)	51 (68.9)	66 (83.5)
Warmer (≥1°C)	24 (27.0)	9 (17.0)	13 (17.6)	6 (7.6)
Colder (≤−1°C)	16 (18.0)	11 (20.8)	11 (14.9)	7 (8.9)
Absolute value (°C) (min-max)	0.2 ± 1.4 (−3.0 to 5.2)	0.0 ± 1.2 (−3.0 to 3.0)	0.5 ± 1.2 (−6.0 to 3.0)	−0.09 ± 0.8 (−3.4 to 2.7)
Skin color sign				
Normal	17 (19.1)	19 (35.8)	39 (52.7)	62 (78.5)
Reddish	43 (48.3)	18 (33.3)	17 (23.0)	8 (10.1)
Pale	3 (3.4)	3 (5.6)	5 (6.8)	2 (2.5)
Bluish	14 (15.7)	8 (14.8)	9 (12.2)	4 (5.1)
Mottled	12 (13.5)	6 (11.1)	4 (5.4)	3 (3.8)
Sudomotor sign				
Sweating	17 (19.1)	3 (5.7)	5 (6.8)	3 (3.8)
Swelling	80 (89.9)	41 (75.5)	48 (64.9)	34 (43.0)
Trophic signs				
None	39 (43.8)	29 (54.7)	54 (73.0)	66 (83.5)
Skin disturbance	13 (14.6)	8 (15.1)	7 (9.5)	5 (6.3)
Hypertrichosis	27 (30.3)	10 (10.4)	4 (5.4)	4 (5.1)
Hypotrichosis	3 (3.4)	2 (3.8)	3 (4.1)	1 (1.3)
Fingernails abnormalities	28 (31.5)	14 (26.4)	12 (16.2)	7 (8.9)
Ulcer	1 (1.1)	1 (1.9)	1 (1.4)	0 (0)
Motor signs				
None	2 (2.2)	3 (5.7)	7 (6.5)	20 (25.3)
Tremor	7 (7.9)	1 (1.9)	2 (2.7)	1 (1.3)
Dystonia	2 (2.2)	0 (0.0)	0 (0)	1 (1.3)
Restricted RoM	84 (94.4)	48 (90.6)	65 (87.8)	56 (70.9)
Weakness	82 (92.1)	39 (73.6)	51 (68.9)	44 (55.7)
Relative strength of the affected side (%)				
UE	0.38 ± 0.28 ($n = 34$)	0.62 ± 0.24 ($n = 24$)	0.63 ± 0.27 ($n = 36$)	0.74 ± 0.30 ($n = 47$)
LE	0.68 ± 0.23 ($n = 26$)	0.84 ± 0.21 ($n = 12$)	0.85 ± 0.21 ($n = 26$)	0.87 ± 0.27 ($n = 31$)
r-bath-CRPS-BPDS (/47)	15.1 ± 8.2	11.2 ± 8.0	10.5 ± 8.8	9.9 ± 9.4
Visuospatial test				
PSS (ms)	3.3 ± 22.3 ($n = 73$)	3.5 ± 29.1 ($n = 49$)	0.5 ± 23.5 ($n = 67$)	5.1 ± 28.9 ($n = 71$)
Slope	0.04 ± 0.04 ($n = 73$)	0.05 ± 0.06 ($n = 49$)	0.13 ± 0.77 ($n = 67$)	0.05 ± 0.05 ($n = 71$)
Variables	**n (%) or mean ± SD**			
	Inclusion ($n = 113$)	**4.5 mo ($n = 65$)**	**6 mo ($n = 86$)**	**1 y ($n = 106$)**
Treatment				
No treatment	0 (0)	8 (12.3)	16 (18.6)	48 (45.3)

(*continued on next page*)

Table 2 (*continued*)

Variables	n (%) or mean ± SD			
	Inclusion (n = 113)	4.5 mo (n = 65)	6 mo (n = 86)	1 y (n = 106)
Paracetamol or NSAIDS	70 (61.9)	21 (32.3)	30 (34.9)	21 (19.8)
Weak opioids	28 (24.8)	9 (13.8)	9 (10.5)	8 (7.5)
Strong opioids	3 (2.7)	2 (3.1)	2 (2.3)	2 (1.9)
Atypical analgesics	15 (13.3)	7 (10.8)	10 (11.6)	11 (10.4)
Topical analgesics	3 (2.7)	4 (6.2)	5 (5.8)	3 (2.8)
Glucocorticoids	12 (10.6)	0 (0)	1 (1.2)	1 (0.9)
Bisphosphonates	6 (5.3)	4 (6.2)	3 (3.5)	2 (1.9)
Physiotherapy (any modality)	104 (92.0)	47 (72.3)	57 (66.3)	42 (39.6)
Active physiotherapy	72 (63.7)	47 (72.3)	57 (66.3)	32 (30.2)
Passive physiotherapy	91 (80.5)	42 (64.6)	43 (50.0)	31 (29.2)
Mirror therapy	17 (15.0)	13 (20.0)	8 (9.3)	6 (5.7)
Psychotherapy	2 (1.8)	4 (6.2)	7 (8.1)	7 (6.6)
Multidisciplinary management	12 (10.6)	12 (18.5)	12 (14.0)	8 (7.5)
Interventional therapy	1 (0.9)	0 (0)	0 (0)	0 (0)
Surgery of the initially affected limb	2 (1.8)	/	/	11 (10.5)

For participants assessed remotely, research Budapest criteria were considered when they reported at least 1 symptom in the 4 categories of the IASP criteria.
CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower extremity; r-Bath-CRPS-BPDS, revised-Bath-CRPS-Body Perception Disturbance Scale; PSS, point of subjective simultaneity.

Table 3

Questionnaires filled at home (with the exception of outcomes).

Variables	n (%) or mean ± SD				*P*
	Inclusion (n = 113)	4.5 mo (n = 82)	6 mo (n = 107)	1 y (n = 105)	
General self-rated health (n = 105 for inclusion)					<0.001
Excellent	4 (3.8)	3 (3.8)	5 (4.7)	3 (2.8)	
Very good	9 (8.6)	15 (18.8)	20 (18.7)	24 (22.4)	
Good	36 (34.3)	26 (32.9)	33 (30.8)	38 (35.5)	
Fair	31 (29.5)	26 (32.9)	33 (30.8)	26 (24.1)	
Poor	25 (23.8)	9 (11.4)	16 (15.0)	16 (15.0)	
Pain-related fear of movement (/44)	31.0 ± 6.7	28.8 ± 7.5	28.7 ± 7.9	26.8 ± 8.4	<0.001
HADS anxiety					
Potential disorder (≥8)	70 (61.9)	43 (52.4)	53 (49.5)	49 (45.8)	<0.001
Probable disorder (≥11)	43 (38.4)	25 (30.5)	33 (30.8)	32 (29.9)	NS
Score (/21)	9.4 ± 4.3	8.4 ± 4.2	8.0 ± 4.2	7.7 ± 4.2	<0.001
HADS depression					
Potential disorder (≥8)	48 (42.5)	33 (40.2)	33 (30.8)	30 (28.3)	0.002
Probable disorder (≥11)	29 (25.7)	17 (20.7)	22 (20.6)	12 (11.3)	<0.001
Score (/21)	7.2 ± 4.4	6.2 ± 4.4	6.4 ± 4.5	5.7 ± 4.4	<0.001
OMPSQ-SF					
Total score (/100)	49.6 ± 17.9	42.6 ± 20.1	43.4 ± 19.6	38.8 ± 21.1	<0.001
Psychosocial risk of chronification					<0.001
Low	34 (30.1)	35 (42.7)	44 (41.5)	56 (52.3)	
Medium	20 (17.7)	15 (18.3)	19 (17.9)	15 (14.0)	
High	59 (52.2)	32 (39.0)	43 (40.6)	36 (33.6)	
Coping strategies to deal with pain					
Distraction (/4)	2.7 ± 0.7	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	NS
Catastrophizing (/4)	1.9 ± 0.6	1.8 ± 0.6	1.9 ± 0.7	1.8 ± 0.7	<0.001
Ignoring painful sensations (/4)	2.1 ± 0.6	2.3 ± 0.7	2.2 ± 0.7	2.4 ± 0.8	<0.001
Distancing from pain (/4)	1.7 ± 0.7	1.7 ± 0.7	1.7 ± 0.7	1.8 ± 0.7	NS
Praying (/4)	1.9 ± 0.9	1.8 ± 0.9	1.8 ± 0.9	1.7 ± 0.9	<0.001
Perceived social support					
Availability (0-54)	24.9 ± 14.4	25.1 ± 14.9	23.6 ± 14.6	23.7 ± 14.3	NS
Satisfaction (6-36)	29.0 ± 7.3	29.0 ± 7.5	28.8 ± 7.7	29.1 ± 7.3	NS
Pain sensitivity					
Total score (/10)	5.0 ± 1.9	5.0 ± 1.9	5.4 ± 2.0	5.0 ± 2.0	0.040
Minor score (/10)	3.8 ± 2.0	3.8 ± 2.0	4.2 ± 2.2	3.8 ± 2.1	0.024

P expressed the significance of the factor "time" (corresponding to each time point) in simple mixed-effect models only including the time as predictors.
CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower extremity; EQ, EuroQol; VAS, visual analogue scale; HADS, hospital anxiety depression scale; OMPSQ-SF, Örebro Musculoskeletal Pain Screening Questionnaire-short form; NS, not significant.

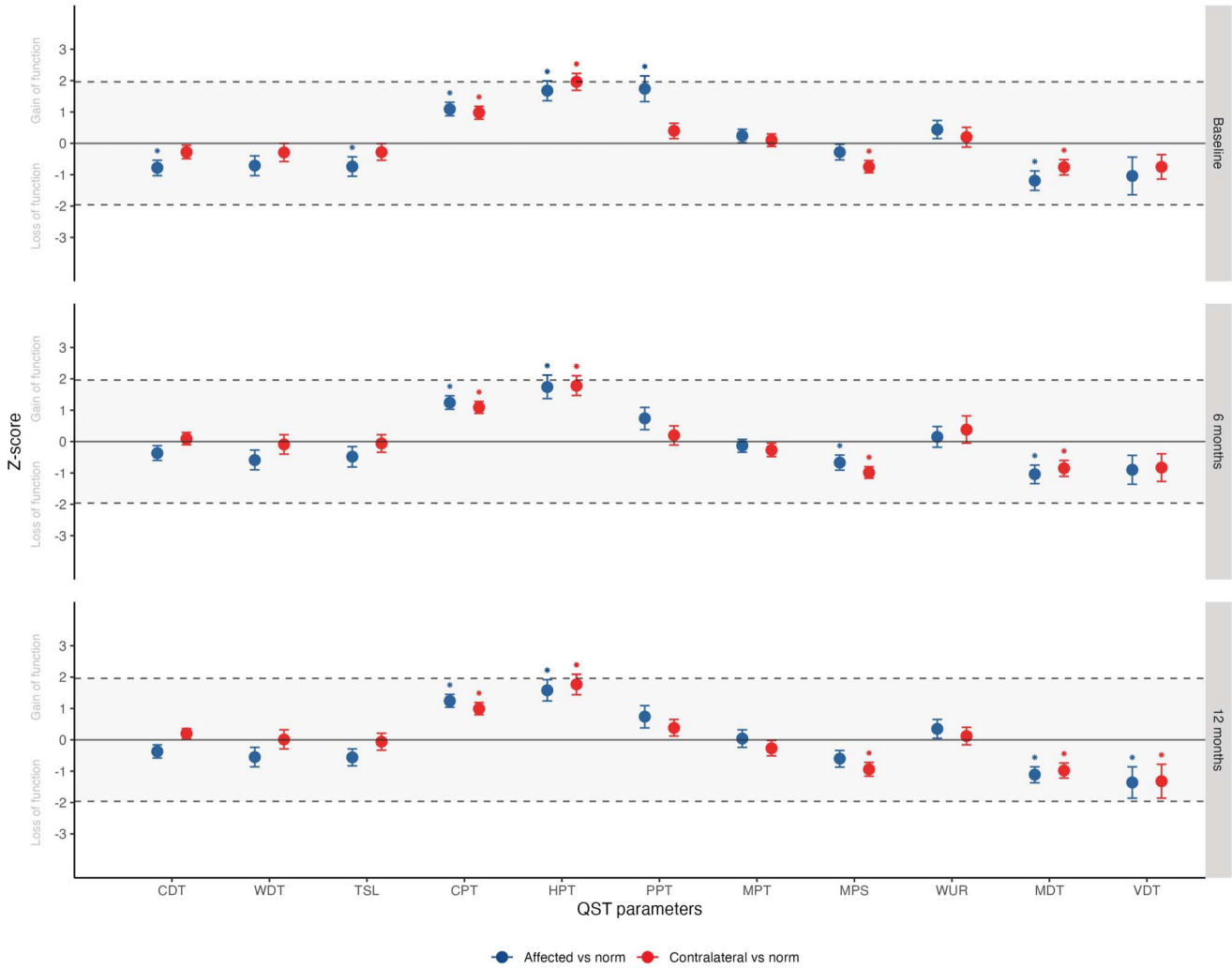

Figure 4. Z-scores of each QST modality at different time points. Mean and CI95. Values from the affected limb and the contralateral side were normalized by the normative values (in blue and red, respectively).[48] *P value < 0.05 after Bonferroni correction; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; PHS, paradoxical heat sensation; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; DMA, dynamic mechanical allodynia; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

to the presence or absence of Budapest clinical criteria at 1 year is available in the supplementary section (6. Supplementary tables—Table S3, http://links.lww.com/PAIN/C392).

On average, we observed a progressive improvement of CRPS, although complete resolution was not achieved in most of the participants. At 1 year, 35% of the cohort still met the clinical Budapest criteria, with a mean CSS of 5.8. The average reported pain (either intensity or interference) remained above 3/10. Disability scores showed persistent impairment at the cohort level, and overall, QoL remained affected. Finally, the large SD for each outcome underlines the considerable variability among the outcomes of patients with CRPS.

To better characterize the impact of CRPS on QoL, we compared EQ-5D-5L results from our cohort (both at baseline and at the 1-year follow-up) with Belgian normative data[61] and with a cohort of patients with chronic pain (symptom duration >12 months) followed in primary care settings[40] (see supplementary material, Table S11, supplemental digital content). Compared with normative values, all CRPS subgroups (early, persistent, and whole cohort at 12 months) showed significantly worse outcomes across all EQ-5D-5L dimensions, EQ index, and EQ VAS ($P < 0.001$; *Chi-squared test and independent t test*). When compared with primary care patients with chronic pain, early and persistent CRPS participants reported greater difficulties in self-care and usual activities ($P < 0.001$, *Chi-squared test*) than patients with chronic pain. At 12 months, the EQ-5D-5L dimensions of the whole CRPS cohort were similar to those of the chronic pain cohort, except for lower pain/discomfort and anxiety/depression. EQ index and EQ-VAS scores remained lower in early and persistent CRPS compared with other patients with chronic pain ($P < 0.05$, *independent t test*), whereas the overall 12-month CRPS cohort showed no significant difference, suggesting partial recovery over time.

Regarding working status (**Table 6**), 61.5% of people who had been active before CRPS onset had returned to work at 6 months, and 69% (n = 48/70) at 1 year. Among participants who returned to work, 13% (n = 6) had reduced the physical demands of their work, and 2 took a part-time job due to CRPS.

Finally, we investigated the clinical evolution of CRPS participants according to their *BE-CRPS profiles,* formerly identified with an LCA analysis,[41] represented in **Figure 6**. **Table 7** presents the outcomes of participants at 12 months, depending on this classification.

First, we observed a similar improvement for all outcomes (ie, similar slopes) regardless of the profile (*effect of the interaction of*

Table 4

Z-scores of each QST modality at different time points.

QST modalities	T1 ($n = 80$)		T3 ($n = 69$)		T4 ($n = 74$)		Time	Side	Time × side
	Aff	Cont	Aff	Cont	Aff	Cont			
	Mean ± SD						*P*		
CDT	−0.78 ± 1.37	−0.28 ± 1.18	−0.37 ± 1.17	0.09 ± 0.97	−0.37 ± 1.08	0.2 ± 0.86	**<0.001**	**<0.001**	0.890
WDT	−0.71 ± 1.73	−0.29 ± 1.59	−0.59 ± 1.61	−0.09 ± 1.57	−0.55 ± 1.6	0.01 ± 1.59	**0.024**	**<0.001**	0.858
TSL	−0.74 ± 1.65	−0.28 ± 1.44	−0.48 ± 1.63	−0.06 ± 1.4	−0.56 ± 1.39	−0.06 ± 1.41	**0.009**	**<0.001**	0.963
PHS (%)	11.2%	8.7%	17.4%	1.4%	11%	5.5%	0.815	**<0.001**	0.180
CPT	1.09 ± 1.19	0.98 ± 1.15	1.24 ± 1.1	1.09 ± 0.95	1.24 ± 1.07	0.99 ± 1.02	0.148	**0.004**	0.833
HPT	1.68 ± 1.75	1.96 ± 1.5	1.74 ± 1.9	1.78 ± 1.59	1.58 ± 1.76	1.77 ± 1.71	0.645	**0.017**	0.766
MDT	−1.19 ± 1.7	−0.76 ± 1.33	−1.04 ± 1.49	−0.85 ± 1.27	−1.11 ± 1.33	−0.98 ± 1.26	0.243	**0.001**	0.238
MPT	0.24 ± 1.15	0.1 ± 1.1	−0.13 ± 1.03	−0.27 ± 1.08	0.04 ± 1.45	−0.27 ± 1.3	**0.007**	0.067	0.535
MPS	−0.28 ± 1.38	−0.75 ± 1.07	−0.67 ± 1.22	−0.99 ± 0.94	−0.6 ± 1.41	−0.94 ± 1.16	**0.002**	**<0.001**	0.684
DMA									
Log	−0.85 ± 0.50	−1 ± 0	−0.89 ± 0.47	−1 ± 0	−0.87 ± 0.51	−1 ± 0	0.766	**<0.001**	0.141
%	12.3%	0%	5.7%	0%	6.7%	0%	0.151	**<0.001**	**0.017**
WUR	0.44 ± 1.29	0.2 ± 1.27	0.15 ± 1.3	0.38 ± 1.56	0.35 ± 1.19	0.12 ± 1.01	0.820	0.436	0.127
VDT	−1.04 ± 3.32	−0.75 ± 2.16	−0.9 ± 2.36	−0.83 ± 2.27	−1.36 ± 2.63	−1.32 ± 2.86	**<0.001**	0.737	0.523
PPT	1.74 ± 2.28	0.4 ± 1.38	0.74 ± 1.85	0.2 ± 1.59	0.74 ± 1.89	0.38 ± 1.41	**<0.001**	**<0.001**	**0.002**

PHS and DMA are expressed as a proportion of subjects showing abnormalities; other values correspond to mean and standard deviation of CRPS participants, normalized using normative values of healthy subjects (Magerl et al., 2010). *P* values expressed the potential effect of time (as a factor), side, and their interaction on the different QST variables (mixed-effect models with random intercept and fixed slope, using the 4 time-point assessments, without imputation). Significant *P*-values are indicated in bold.

QST, quantitative sensory testing; T1, inclusion; T3, 6 mo; T4, 1 y; n, number of participants with fully assessed QST. Part of the modalities were collected for 15 others. Aff, affected side; Cont, contralateral side; Time x Side, interaction between time and side; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; PHS, paradoxical heat sensation; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; DMA, dynamic mechanical allodynia; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

time x outcomes in LMMs: $P > 0.05$). Second, their outcomes remain distinct at every time point (*Kruskal-Wallis Test for every outcome at each time point: $P < 0.05$*). At 12 months, this difference was most prominent between the *Mild* profile and the severe profiles (ie, *BRD* and *Pressure allodynia CRPS*), the latter profiles reporting the poorest outcomes at 1 year, still more pejorative than the values of *Mild* or even *Moderate CRPS* profiles at inclusion (**Table 7**).

It should be noted that the proportion of participants who returned to work at 12 months was not significantly different between the profiles.

3.3. Early prognostic factors in complex regional pain syndrome

3.3.1. General considerations

Owing to its length, the description of the potential predictive value of each variable in a simple multivariable model (see the Methods section for further details) is available upon request or through the following link (https://osf.io/5qz2w/?view_only=7d52ddac7e124297ab38c0b1f463bcd4). In the following sections, we only present the final multivariable models (**Table 8**).

Table 5

Evolution of the outcomes over 1-year period.

Variables	*n* (%) or mean ± SD			
	Inclusion ($n = 113$)	4.5 mo ($n = 82$)	6 mo ($n = 107$)	1 y ($n = 107$)
Body function and structures				
CRPS severity score (/16)	11.5 ± 2.2 ($n = 89$)	8.9 ± 2.9 ($n = 53$)	8.1 ± 3.2 ($n = 74$)	5.8 ± 4.0 ($n = 79$)
Meeting Budapest clinical criteria	113 (100.0)	35 (53.8) ($n = 64$)	43 (50.0) ($n = 86$)	37 (34.9) ($n = 105$)
Pain intensity (/10)	4.7 ± 2.3	4.1 ± 2.3	4.1 ± 2.4	3.8 ± 2.6
Activities				
Pain interference (/10)	4.9 ± 2.3	3.6 ± 2.5	3.8 ± 2.7	3.2 ± 2.7
Disability				
Z score	0 ± 1	−0.79 ± 1.13	−0.94 ± 1.14	−1.46 ± 1.13
UE (/100)	62.6 ± 19.3 ($n = 67$)	49.2 ± 20.7 ($n = 47$)	45.5 ± 21.2 ($n = 64$)	34.8 ± 21.6 ($n = 63$)
LE (/80)	47.2 ± 15.6 ($n = 46$)	32.9 ± 18.8 ($n = 35$)	31.2 ± 18.9 ($n = 43$)	23.9 ± 17.9 ($n = 44$)
Participation				
Quality of life				
EQ index (/1)	0.51 ± 0.30	0.64 ± 0.28	0.68 ± 0.26	0.74 ± 0.24
EQ VAS (/100)	53.0 ± 21.5	63.5 ± 19.7	64.7 ± 21.0	69.8 ± 19.6

CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower extremity; EQ, EuroQol; VAS, visual analogue scale.

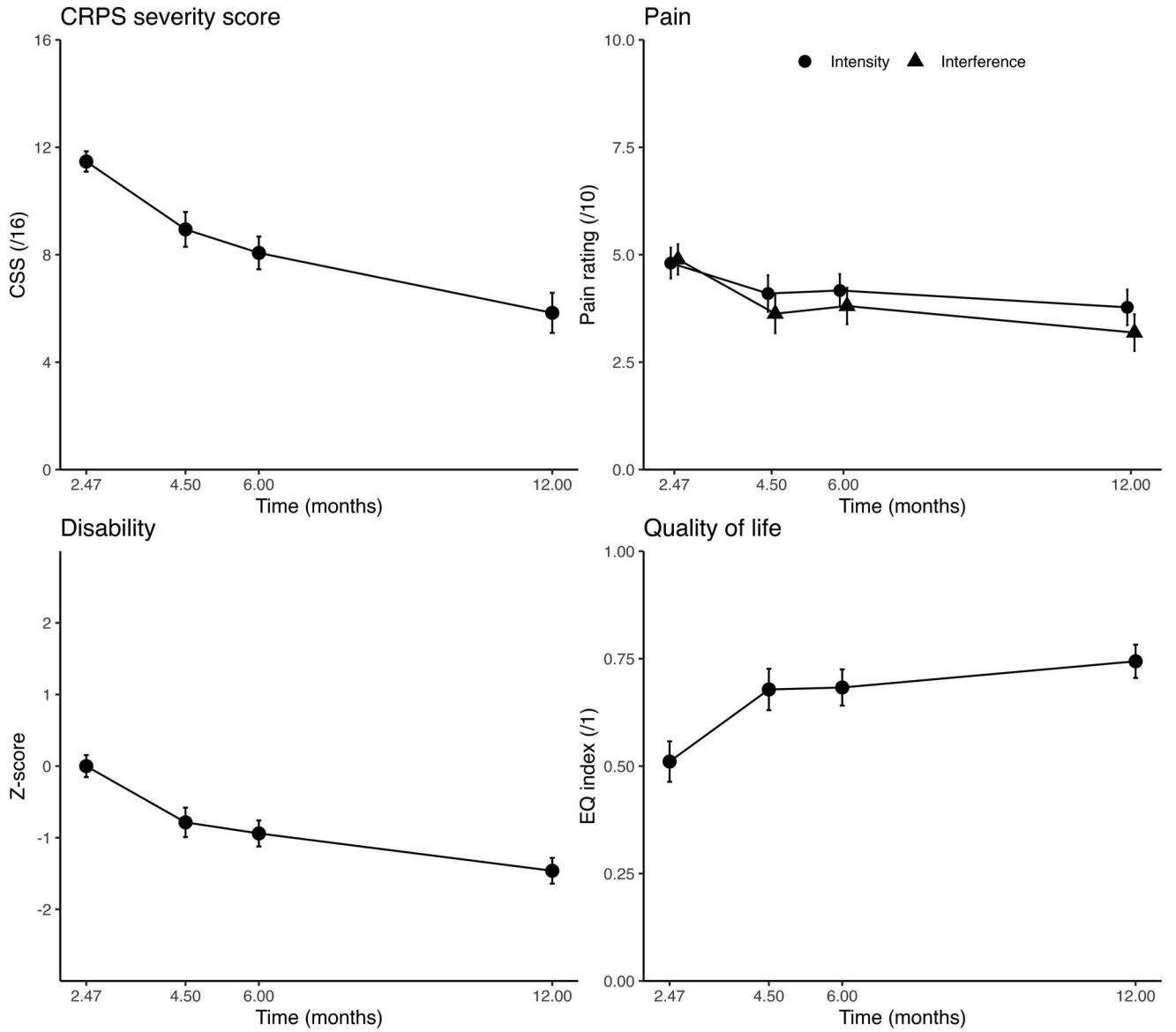

Figure 5. Evolution of the different continuous outcomes for the whole sample. Mean and CI95. For graphical representation, the starting point was considered as the mean CRPS duration at inclusion (2.47 months).

Given their potential subtending pathophysiological mechanisms and clinical applications (eg, therapeutic targets), we chose to include the *BE-CRPS profiles* in the multivariable analyses. Therefore, the 5 variables used to design the profiles (ÖMPSQ, r-B-CRPS-BPDS, presence of allodynia, physical intensity of the triggering event, and PPT of the affected limb) were not considered as separate potential predictors. It should be noted that many biopsychosocial variables were highly associated with CRPS evolution in the *univariate* analyses (eg, pain-related fear of movement, catastrophizing, ÖMPSQ, depressive and anxiety disorders, pain, general self-rated health, EQ index and EQ VAS, etc). As ÖMPSQ has been already used to create the profiles, the disability score was chosen as an *umbrella* variable for biopsychosocial factors, gathering several concepts and strongly correlated with others meaningful biopsychosocial predictors. Furthermore, it was put forward as a potential early prognostic factor in previous research.[42]

Regarding early treatment, our protocol was not designed to assess the potential predictive value of therapeutic modalities.[52] For instance, some analgesics were associated with poorer outcomes (as already described in 4); it was probably a reflection of the severity of the condition rather than a prognostic factor in itself. Surprisingly, vitamin C (n = 55) was associated with reduced pain over time in the simple multivariable models, while participants doing physiotherapy (n = 104) at inclusion presented an improvement of certain outcomes over time in comparison to the other subjects. More specifically, this association was observed with strengthening and stretching modalities rather than TENS or passive physiotherapy (eg, massage). Other early therapeutic modalities showed no impact on the prognosis (eg, glucocorticoids [n = 12], bisphosphonates [n = 6], mirror therapy [n = 17], or multidisciplinary management [n = 12]). Nevertheless, owing to the inherent bias in the assessment method (self-reporting, assessed at a specific time point) and the potential confounding effect with other predictors, the treatment variables were not included in the final multivariable analyses.

Table 6

Work status of participants previously working before CRPS onset, during the follow-up period.

Variables	*n* (%) or mean ± SD			
	Inclusion (*n* = 77)	4.5 mo (*n* = 55)	6 mo (*n* = 65)	1 y (*n* = 70)
Has returned to work (%)	23 (29.9)	29 (52.7)	40 (61.5)	48 (68.6)
Working status (%)				
Worker	18 (23.4)	25 (45.5)	34 (52.3)	46 (65.7)
Medical part-time	5 (6.5)	4 (7.3)	6 (9.2)	2 (2.9)
Pensioner	3 (3.9)	0 (0)	1 (1.4)	2 (2.9)
Student	2 (2.6)	2 (3.6)	1 (1.4)	2 (2.9)
Unemployed	1 (1.3)	2 (3.6)	1 (1.5)	2 (2.9)
Sickness	48 (62.3)	22 (40.0)	22 (33.8)	16 (22.9)

CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants assessed at particular time point (among those working prior to the CRPS onset).

3.3.2. Predictors of complex regional pain syndrome severity score and clinical Budapest criteria (body function and structure in the International Classification of Functioning, Disability and Health)

The following variables were independently associated with CSS regardless of the time point: *baseline CSS*, *baseline disability*, and *BE-CRPS profiles*. The model explained 48% of the variance of the dependent variable. In brief, *severe BE-CRPS profiles*, higher *CSS,* and *disability* at an early stage were associated with higher CSS at every time point.

For the presence or absence of clinical Budapest criteria at 12 months, *BE-CRPS profiles* (severe profiles [*BRD* or *Pressure allodynia CRPS*] in comparison with *Mild CRPS*), and *BMI* were independent predictors of this dichotomic outcome in a logistic

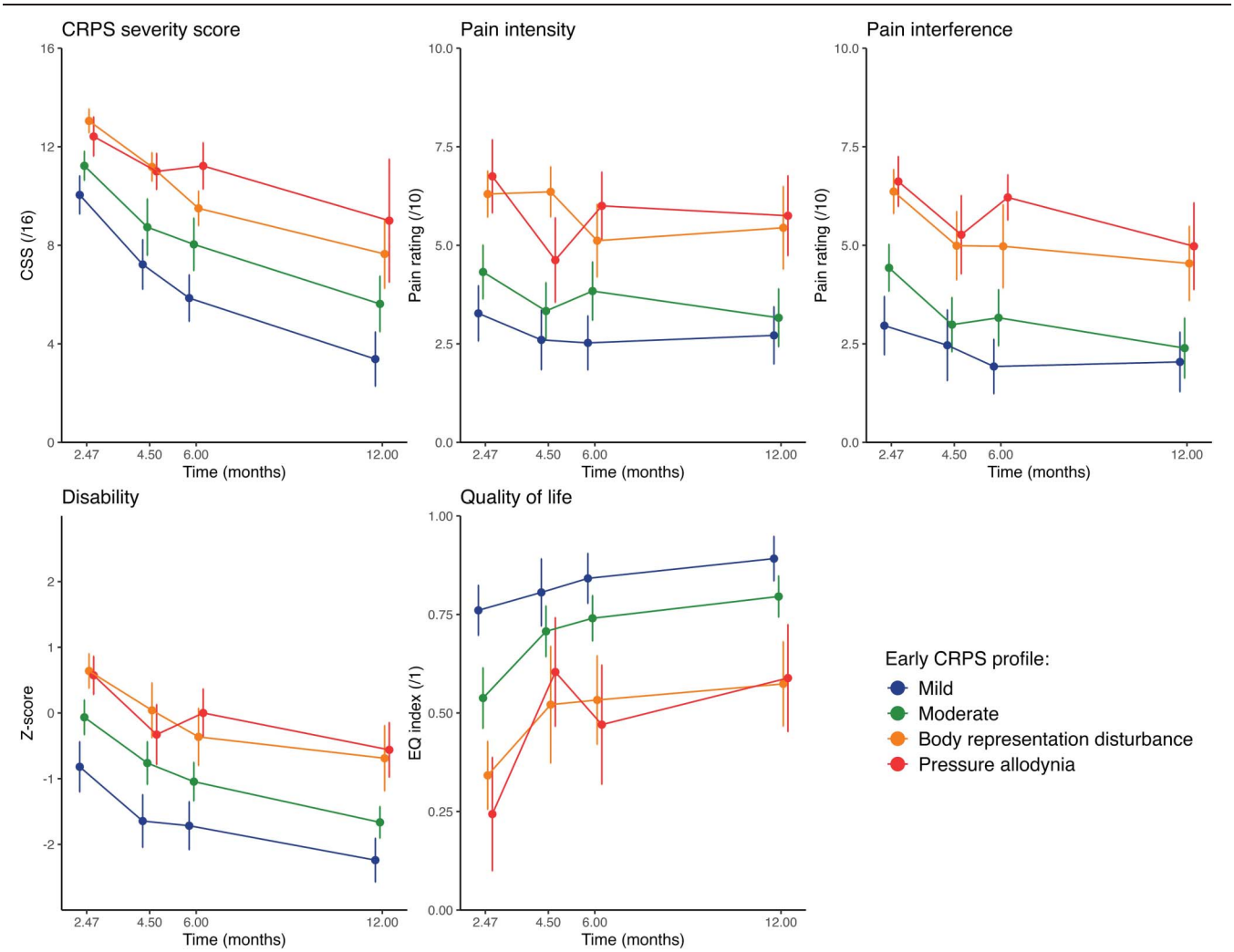

Figure 6. Evolution of each Biopsychosocial Early CRPS (BE-CRPS) profile. Mean and CI95. For graphical representation, the starting point was considered as the mean CRPS duration at inclusion (2.47 months).

Table 7

Outcomes at 1 y according to early CRPS profiles.

Variables	n (%) or mean ± SD				*P*
	Mild CRPS (*n* = 21)	Moderate CRPS (*n* = 31)	Severe CRPS (*n* = 30)		
			BRD CRPS (*n* = 18)	Pressure allodynia CRPS (*n* = 12)	
Body function and structures					
CRPS severity score (/16)	3.4 ± 3.1†□ (*n* = 21)	5.6 ± 3.7 (*n* = 29)	7.7 ± 3.5† (*n* = 17)	9.0 ± 4.8□ (*n* = 10)	**<0.001**
Clinical Budapest criteria	2 (9.5)†□	6 (19.4)■§	12 (66.7)†§	8 (66.7)□■	**<0.001**
Pain intensity (/10)	2.7 ± 2.0†□	3.2 ± 2.5■§	5.4 ± 2.7†§	5.8 ± 2.1□■	**<0.001**
Activities					
Pain interference (/10)	2.0 ± 2.1†□	2.4 ± 2.6■§	4.5 ± 2.4†§	5.0 ± 2.3□■	**<0.001**
Disability					
Z score	−2.24 ± 0.93†□	−1.66 ± 0.81■	−0.69 ± 1.28†	−0.56 ± 0.88□■	**<0.001**
UE (/100)	24.1 ± 19.2†□ (*n* = 15)	31.9 ± 17.7 (*n* = 18)	50.7 ± 23.5† (*n* = 10)	55.9 ± 8.1□ (*n* = 5)	**0.004**
LE (/80)	2.7 ± 3.3†□ (*n* = 10)	19.5 ± 10.3 (*n* = 13)	35.0 ± 22.4† (*n* = 8)	36.0 ± 17.3□ (*n* = 7)	**0.002**
Participation					
Quality of life					
EQ index (/1)	0.89 ± 0.16†□	0.80 ± 0.18	0.57 ± 0.28†	0.59 ± 0.29□	**<0.001**
EQ VAS (/100)	78.7 ± 16.4□	69.4 ± 22.1	68.1 ± 17.6	56.9 ± 20.5□	**0.013**
Return to work	12 (80.0) (*n* = 15)	17 (73.9) (*n* = 23)	8 (66.7) (*n* = 12)	2 (28.6) (*n* = 7)	0.093

The *P* values correspond to the Kruskal-Wallis or Chi-squared test. Significant *P*-values are indicated in bold.
† or □ or ■, significant pairwise comparisons between BE-CRPS profiles (adjusted by the Bonferroni correction); CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; BRD, body representation disturbance; UE, upper extremity; LE, lower extremity; EQ, EuroQol; VAS, visual analogue scale.

regression model. In summary, *higher BMI* and *severe BE-CRPS profiles* were linked to a greater likelihood of still meeting Budapest criteria after 1 year.

3.3.3. Predictors of pain intensity (body function and structure in the International Classification of Functioning, Disability and Health)

Baseline pain intensity score, *BE-CRPS profiles*, *BMI*, and *baseline CSQ ignoring painful sensations* appeared to be independent early prognostic factors in the multivariable model. Fifty percent of pain intensity variance was explained by these variables. In short, individuals with *Mild CRPS profile*, *lower BMI*, and a *tendency to disregard painful sensations* reported lower pain ratings at each assessment.

3.3.4. Predictors of pain interference (activities in International Classification of Functioning, Disability and Health)

Two variables were enough to explain 45% of the variance of pain interference evolution regardless of the time point: *baseline pain interference score* and *BE-CRPS profiles*.

3.3.5. Predictors of disability (activities in International Classification of Functioning, Disability and Health)

Baseline disability score, *BMI*, and *social support (availability)* were identified as independent early prognostic factors. The model explains 66% of the disability variance through the 4 time points. To put it succinctly, *higher disability*, *BMI,* and *lower social support* at baseline were associated with higher disability during 1-year follow-up.

3.3.6. Predictors of quality of life (participation in International Classification of Functioning, Disability and Health)

Four variables were independently associated with the QoL regardless of the time point: *BMI*, *baseline EQ index*, *disability*, and *anxiety scores*. The model explains 54% of the QoL variance. Overall, a *lower EQ index*, along with *higher disability*, *anxiety*, and *BMI*, was a predictor of reduced quality of life at each time point.

3.3.7. Predictors of return to work (participation in International Classification of Functioning, Disability and Health)

As the *BE-CRPS profiles* were not influencing RtW in the *univariate* logistic regression model, we included the variables initially used to create the profiles (if they were significant in preliminary simple multivariable models). We identified that the baseline *ÖMPSQ score* was the only independent variable associated with the likelihood of returning to work during the first year following the CRPS onset.

3.3.8. Models without biopsychosocial early complex regional pain syndrome profiles

To evaluate whether the *BE-CRPS profiles* had an added value to predict evolution when compared with more *classical* predictors, we also ran the analysis where profile data were replaced by the 5 variables used to generate the *BE-CRPS profiles*. For the sake of completeness, we have presented these models in the supplementary sections (6. Supplementary tables – Table S9). We observed a significant predictive value of the *ÖMPSQ score* for all outcomes, and of the *presence of allodynia* for some. The identified prognostic factors and percentage of explained variance were similar to the models including the *BE-CRPS profiles*.

3.3.9. Variables with an absence of evidence

In **Table 9**, we regrouped the variables with an absence of significant prognostic value ($P > 0.010$), in simple multivariable models for any of the tested outcomes. Among others, initial *skin temperature* was not associated with any outcome.

Table 8

Early prognostic factors identified in multivariable analyses.

Prognostic factors (values at T1)	Outcomes																										
	Body structure and function												Activities								Participation						
	CRPS severity score				Clinical Budapest criteria			Pain intensity					Pain interference				Disability				Quality of life				Return to work (ÖMPSQ model)		
	β^{Std}	β	SE	*P*	OR	95 CI	*P*	β^{Std}	β	SE	*P*		β^{Std}	β	SE	*P*	β^{Std}	β	SE	*P*	β^{Std}	β	SE	*P*	OR	95 CI	*P*
Time (mo)	/	−0.729	0.134	**<0.001**		Not included		/	−0.181	0.080	**0.024**		/	−0.314	0.080	**<0.001**	/	−0.252	0.028	**<0.001**	/	0.051	0.008	**<0.001**		*Not included*	
Time^2 (mon^2)	/	0.018	0.010	**<0.001**		Not included		/	0.007	0.006	0.251		/	0.012	0.006	**0.033**	/	0.009	0.002	**<0.001**	/	−0.002	0.001	**<0.001**		*Not included*	
Age (y)	−0.010	−0.003	0.015	0.862	1.01	0.97-1.05	0.590	0.026	0.005	0.008	0.513		0.039	0.008	0.011	0.462	0.012	0.001	0.004	0.775	−0.111	−0.001	0.001	0.285	0.97	0.92-1.03	0.329
Sex (ref = female)	/	0.473	0.471	0.315	1.26	0.37-4.34	0.717	/	−0.390	0.243	0.113		/	0.127	0.329	0.698	/	−0.021	0.123	0.862	/	−0.034	0.030	0.262	1.13	0.17-7.52	0.150
Limb (ref = UE)	/	0.252	0.410	0.538	0.87	0.40-3.30	0.793	/	0.029	0.214	0.904		/	0.076	0.296	0.798	/	0.022	0.111	0.842	/	−0.033	0.027	0.213	0.89	0.90-0.97	0.401
Baseline values																											
Outcome variable	0.162	0.294	0.098	**0.003**	/	/ /	/	0.504	0.570	0.052	**<0.001**		0.592	0.592	0.077	**<0.001**	0.718	0.818	0.051	**<0.001**	0.618	0.494	0.058	**<0.001**	/	/ / /	
Disability	0.177	0.706	0.229	**0.002**																	−0.158	−0.038	0.017	**0.024**		Not included	
Early CRPS profiles (ref = Mild CRPS)																											
Moderate CRPS	/	0.587	0.533	0.271	1.85	0.40-9.19	0.454	/	0.180	0.287	0.530		/	0.208	0.400	0.603										Not included	
BRD CRPS	/	1.450	0.650	**0.026**	11.58	2.15-62.22	**<0.001**	/	0.896	0.330	**0.007**		/	0.899	0.481	0.062											
Pressure allodynia CRPS	/	1.834	0.720	**0.011**	9.49	1.58-56.80	**0.016**	/	0.853	0.377	**0.024**		/	1.302	0.533	**0.015**											
BMI					1.21	1.01-1.24	**0.031**	0.100	0.053	0.022	**0.012**						0.108	0.025	0.010	**0.014**	−0.123	−0.006	0.003	**0.019**			
CSQ ignoring painful sensations								−0.099	−0.427	0.171	**0.015**																
SSQ availability																	−0.114	−0.009	0.004	**0.011**							
HADS anxiety score																					−0.143	−0.008	0.003	**0.013**			
ÖMPSQ score		Not included				Not included			Not included					Not included				Not included				Not included			0.96	0.93-0.99	**<0.001**
R^2 (MVP)		**0.482**				/			**0.505**					**0.447**				**0.664**				**0.538**				/	

Linear mixed models with random intercept and time, time^2.

Age, sex, and limb and relevant variable(s) (see the Methods section for selection) as fixed factors in each model, with the exception of binary outcome, where a binary logistic regression was performed. Time was therefore not included as a covariate in these 2 models. The "outcome variable" corresponded to the baseline value of the investigated outcome (eg, for pain intensity, the baseline pain intensity; see the Methods section for details). "Blank section" referred to variables that were removed during the selection stage.

T1, inclusion; β^{Std}, estimate standardized; β, estimate; SE, standard error; *P*: *P* value in final multivariate model; OR, odds ratio; 95 CI, 95% confidence interval (lower-upper); RtW, return to work; ref, reference value; UE, upper extremity; BMI, body mass index; CSQ, Coping Strategies Questionnaire; SSQ, Social Support Questionnaire; HADS, Hospital Anxiety Depressive Scale; ÖMPSQ, Örebro Musculoskeletal Pain Screening Questionnaire; Not included, not included in the multivariate model for theorical and statistical reasons (see the Methods section for further explanations); UE, upper extremity; R2 (MVP): proportion of variance of the dependent variable explained by the model.

Table 9

Variables with an absence of evidence in simple multivariate models.

Demographical variables	Age (among adults) Sex Smoking habits (pack-year)
CRPS features	CRPS duration (onset or since triggering event, in d) CSS sign temperature (abnormal vs normal) Skin temperature (continuous) CSS sign skin color (abnormal vs normal) CSS sign motor (present vs absent)
Neurocognitive features	TOJ PSS
CRPS classifications	Family history of CRPS
Psychosocial variables	CSQ distraction PSQ minor PSQ total score
Early treatments	Bisphosphonates (n=6) Glucocorticoids (n=12) Acetylcysteine (n=18) Vitamin D (n=38) Contrast baths (n=32) Mirror therapy (n=17) Passive physiotherapy (n=89) Multidisciplinary management (n=12)
QST modalities (Z-scores)	CDT (control side) WDT (control side) TSL (control side) HPT (affected and control sides) MDT (affected and control side) MPT (affected and control sides) WUR (affected and control sides) VDT (control side)

QST, quantitative sensory testing; CRPS, complex regional pain syndrome; N, number of subjects presenting this characteristic in the inclusion cohort; CSS, CRPS Severity Score; TOJ, Temporal Order Judgement task; PSS, point of subjective simultaneity; CSQ, Coping Strategies Questionnaire; PSQ, Pain Sensitivity Questionnaire; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical painful threshold; WUR, wind-up ratio; VDT, vibration detection threshold.

4. Discussion

We conducted a comprehensive, prospective, observational analysis of 113 patients with early CRPS from different clinical practices, over a 1-year period, with repeated assessments of various biopsychosocial variables. With a high follow-up rate (95%), our findings confirm the evolution described in prior studies.[3,6,34] Prognosis may be influenced by a limited number of independent early factors, including *BMI*, *baseline disability*, *allodynia*, and *ÖMPSQ scores*. Incorporating the latter 2, the *BE-CRPS profiles* were strongly associated with multiple outcomes.

4.1. Clinical evolution

At 1 year, 35% of participants still met the clinical Budapest criteria, and only two-thirds had resumed professional activity (substantially lower than the 89% RtW rate in low back pain 14). Compared with Belgian norms, QoL remained reduced across the whole cohort at 12 months,[61] while patients with persistent CRPS reported worse outcomes than those from a Belgian chronic pain sample managed in primary care.[40] No spreading[22] was observed, and outcomes were similar irrespective of surgery on the affected limb (n = 11), suggesting there is no clear contraindication for performing surgery on a limb with a history or active state of CRPS, provided it is deemed medically necessary.

Interestingly, CRPS duration at baseline did not significantly affect outcomes at any time point, implying that early-stage CRPS (up to 6 months) remains relatively homogeneous based on this criterion, without a minimum time threshold required for diagnosis.

Body perception disturbances remained stable over the 1-year period for participants still meeting Budapest criteria at 1 year, while some variation was observed between baseline and 6 or 12 months in the whole cohort. These results suggest that, for participants who are developing a persistent condition, such disturbances are present from the outset.

Repeated QST assessments showed that most of the sensory modalities changed little over time. Indeed, the only significant differences were found between the measured values at baseline and those at other sessions (4.5, 6, and 12 months) but not between these latter time points, indicating sensory changes mostly concern the first months of CRPS. Previous research, conducted with smaller sample sizes, has suggested that the sensory profile of patients with CRPS remains stable over time.[17,51] Given that both of these studies included patients with longer CRPS durations, our findings align with their results. This suggests that individual sensory profiles tend to quickly stabilize independently of the condition's evolution (ie, resolve or become persistent), limiting the utility of repeated QST assessments as biomarkers of the CRPS evolution.

4.2. Early prognostic factors

In the past, CRPS prognosis research has primarily focused on biological factors, as illustrated by the conclusion of a 2011 Delphi survey.[11] Forty-nine items, such as sensory or motor changes, were deemed to be associated with poorer outcomes. Conversely, only 3 social factors were considered relevant, and psychological factors were surprisingly not mentioned at all. More recent studies have particularly highlighted the crucial role of psychological factors in the development of persistent CRPS.[4,13] There are also numerous studies associating unfavourable psychosocial variables with a more serious state.[1,5,18] It is, however, essential to emphasize that individuals who develop CRPS do not present a distinct psychological profile,[8] and the so-called "*yellow flags*" reflect normal psychological responses to pain rather than underlying psychopathology. As illustrated by the fear-avoidance[62] and pain interpretation bias models,[60] it is the *intensity* and *persistence* of these reactions over time that increase the risk of chronification. Both models support that early interventions might reduce the transition from acute to chronic conditions.[35,59]

Our results show that it might be possible to predict CRPS evolution based on early factors. As for low back pain, prognosis appears to be primarily influenced by psychosocial variables—captured by the ÖMPSQ—and additional factors such as BMI or social support rather than some CRPS-specific features (historical classification [type I vs II], CSS, or skin temperature). Moreover, the presence of allodynia and body perception disturbances, both included in the *BE-CRPS profiles*, also emerged as key prognostic factors. Our results are globally consistent with the existing literature.[42,55] However, whereas previous studies have linked high-energy trauma to a poorer prognosis,[42] our findings indicate the opposite: patients with more intense initial trauma tended to have better outcomes, as suggested by the *BE-CRPS profiles* (where *Mild* and *Moderate* profiles were associated with better outcomes and higher intensity traumatic event)[41] and preliminary simple multivariable analyses.

Body mass index emerged as a relevant prognostic factor in both our study and Román cohort.[55] While obesity is frequently

linked to chronic pain, the exact nature of this relationship remains debated.[29,44,48] In CRPS, 2 possible explanations might be proposed: (1) higher BMI directly contributes to a worse prognosis, potentially due to chronic low-grade inflammation present in patients who are obese,[56] and/or (2) higher BMI reflects a more complex psychosocial burden, not fully captured by including psychosocial measures, despite our extensive assessment of these variables in multivariable models.

The *BE-CRPS profiles*[41] were associated with different outcomes and might independently participate in prognosis. ÖMPSQ score (and, in a minor way, the presence of allodynia) were also strong predictors of CRPS evolution, explaining similar variance in multivariable models. However, considering the *BE-CRPS profiles* as a prognostic factor might add information compared with the ÖMPSQ categories alone. For instance, some participants classified as high risk based on ÖMPSQ were assigned to the *Mild CRPS* profile, while *BRD CRPS* (1 of the severe profiles, associated with the poorest outcomes) had an ÖMPSQ score comparable to *Moderate CRPS*. This suggests that relying solely on the ÖMPSQ may be an oversimplified approach to prognostic stratification.

4.3. Clinical and research perspectives

Our results show that patients with CRPS presenting an initial severe condition are at greater risk of developing a persistent condition. Current data do not allow us to conclude that the use of our *BE-CRPS* profiling has a greater clinical interest than that of each of the variables used to construct these profiles.[35] For clinicians seeking a quick screening, assessment of ÖMPSQ and the presence of allodynia might be sufficient. For the researcher, however, we suggest that classifying patients using these early profiles—and thus incorporating physical intensity of the triggering event, body perception disturbances, and deep tissue sensitivity as additional variables—offers valuable opportunities to advance mechanistic understanding and guide personalized interventions, considering the underlying pathophysiological hypotheses and potential therapeutic targets.[41] **Figure 7** illustrates a putative and unvalidated stratified early management based on *BE-CRPS profiles*, inspired by the last guidelines.[19,21,26] In particular, the 2 severe profiles may benefit from early intensive therapies, including cognitive multisensory interventions targeting body perception disturbances[2] for the *BRD CRPS profile*, while patients belonging to the *Pressure allodynia CRPS profile* might respond better to cognitive behavioural therapy or exposure therapy because of the initial higher ÖMPSQ score. However, these 2 profiles showed comparable characteristics at 12 months, suggesting that this distinction may be more theoretical than clinically actionable. Therefore, rather than targeting psychotherapy to a single profile, we advocate for individualised early psychological support in both severe profiles (even though we expect a greater effect in *Pressure allodynia CRPS*).

To support the implementation of early CRPS profiling, we have made the subgrouping equation publicly available (https://github.com/vladaron/CRPS_longitudinal). Researchers and clinicians can input 5 easily assessed parameters to estimate the probability of a patient belonging to each profile.

4.4. Strengths and limitations

This study presents several strengths: (1) very small drop-out rate (5%), (2) large multicentre cohort performing a comprehensive biopsychosocial assessment, capturing multiple dimensions of the CRPS experience, (3) unsupervised and rigorous selection of potential prognostic factors investigating numerous biopsychosocial concepts, (4) use of transparent and advanced statistical techniques, such as LMMs and multiple imputation, and (5) inclusion of early CRPS profiles in the analyses, potentially more relevant than traditional CRPS subtypes.

One of the limitations concerns the diagnosis of CRPS, which, in a part of the cohort, was not based on direct physical assessment by the investigator. This could have created discrepancies between included participants, as CRPS diagnosis is based on clinical expertise. However, this risk was mitigated by several factors: participants were referred by experienced clinicians using the Budapest criteria, presented typical CRPS history and symptoms, and had outcomes that were consistently collected across all subjects through online questionnaires (except for CSS).

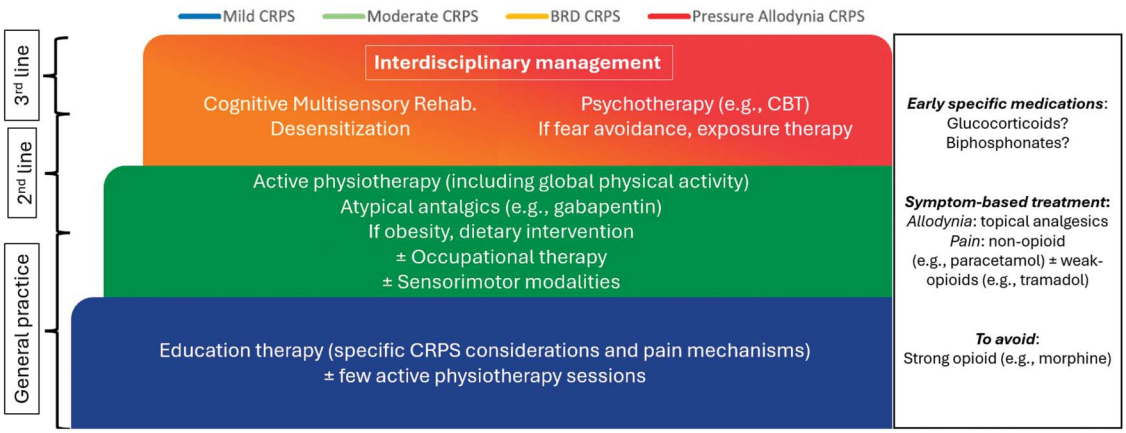

Figure 7. Potential early stratified and personalized management approach based on *BE-CRPS* profiles. This stratification approach aims to optimize healthcare use—enhancing outcomes in more severe cases through early referral and intensive rehabilitation, while avoiding overtreatment in *Mild CRPS*, where conservative general practice may suffice. Based on guidelines,[19, 21, 26] all patients receive a core treatment package (corresponding to *Mild CRPS*, in blue), while additional therapeutic resources are directed to more severe profiles. Although *BRD* and *Pressure allodynia CRPS* were defined by distinct early features, they showed similar characteristics at 12 months. Thus, the distinction may be more theoretical than clinically actionable. Both severe profiles may benefit from personalized, multimodal rehabilitation tailored to individual clinical features rather than fixed, profile-based protocols. Some treatments (eg, glucocorticoids, bisphosphonates) are not assigned to specific profiles but may be beneficial in early CRPS; further research is needed to support routine use.[9,19] Similarly, first- and second-line analgesics should be adapted to patient needs and preferences, while strong opioids are not recommended for chronic pain conditions. CRPS, complex regional pain syndrome; BE-CRPS profiles, Biopsychosocial Early CRPS profiles; BRD, body representation disturbances; Rehab., rehabilitation; CBT, cognitive behavioural therapy.

Furthermore, no significant differences were found in baseline variables or outcomes at 1 year between participants who were assessed remotely and those who underwent face-to-face assessment.

While the sample size is relatively small for exploring a wide range of prognostic factors, the statistical design (LMMs and multiple imputation) enhances confidence in the identified factors. However, it is possible that some predictors deemed insignificant in the multivariable analyses might explain small parts of the variability between participants. The clinical relevance of these predictors remains debatable, given their potential marginal impact on outcomes.

Eventually, the *BE-CRPS profiles* and prognostic factors identified in this study need to be validated in external cohorts. Replication of the findings in larger, independent samples is necessary to confirm their generalizability and utility in clinical practice. Implications for clinical management and secondary prevention of subjects suffering from early CRPS remain to be discussed and explored.

4.5. Conclusions

In this comprehensive prospective study of patients with early CRPS, we aimed to identify early prognostic factors and assess the clinical evolution of the condition over a 1-year period. Our findings confirm the general prognosis associated with CRPS and suggest that a combination of psychosocial assessments, including the ÖMPSQ, alongside basic clinical evaluations, could offer a practical and efficient means of identifying patients at higher risk of more severe outcomes. Future research should focus on refining these early prognostic models, incorporating both biological and psychosocial factors, to enable more personalized and effective management strategies for CRPS.

Conflict of interest statement

The authors have no conflict of interest to declare.

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