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3 1 **Effect of an interdisciplinary inpatient program for patients with CRPS in reducing**
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5 2 **disease activity –a single center prospective cohort study**
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59 26 Running title: Inpatient treatment of CRPS patients.
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1 **ABSTRACT**

2 **Objective:** The aim of this study was to evaluate the benefit of inpatient treatment in reducing
3 disease activity in patients with CRPS who have exhausted outpatient options. Furthermore,
4 the study sought to identify patient-related outcome variables that predict a reduction in
5 disease activity.

6 **Methods:** The primary outcome was disease severity (CRPS Severity Score, range 0 – 16
7 points)). Secondary outcomes included depression, anxiety, physical function, pain
8 interference, fatigue, sleep disturbance, and ability to participate in social roles and activities,
9 all of which were assessed using the Promis-29. Furthermore, pain catastrophizing,
10 neuropathic pain, quality of life, pain self-efficacy, medication intake, and the patient's global
11 impression of change were examined in accordance with current international agreed
12 recommendations, assessed at discharge, three-month and six-month post-discharge. Mixed-
13 effects models were conducted to identify baseline variables associated with CRPS severity.

14 **Results:** Twenty-five patients completed the program (mean age 49.28 (SD 11.23) years, 92%
15 females, mean symptom duration 8.5 (SD 6.5) months). Results showed a significant
16 reduction between baseline and discharge of disease activity (CSS -2.36, $p < 0.0001$), pain
17 (PROMIS-29 pain -0.88, $p = 0.005$) and emotional function (PROMIS-29 depression -5.05,
18 $p < 0.001$; fatigue -4.63, $p = 0.002$). Moderate evidence for a reduction between baseline and
19 discharge could be observed for pain interference (+2.27, $p = 0.05$), social participation
20 (PROMIS-29 +1.93, $p = 0.05$), anxiety (PROMIS-29 -3.32, $p = 0.02$) and physical function
21 (PROMIS-29 +1.3, $p = 0.03$). On discharge, 92% of patients (23 of 25) reported improvement
22 in their overall condition. In the follow-up period, medication intake could be reduced after 3
23 (MQS -8.22, $p = 0.002$) and 6 months (MQS -8.69, $p = 0.001$), and there was further
24 improvement in social participation after 3 months (PROMIS-29 +1.72, 0.03) and sleep after
25 6 months (PROMIS-29 +2.38, 0.008). In the mixed models, it was demonstrated that patients
26 experiencing less pain at baseline also exhibited lower disease activity.

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1 **Conclusion:** The results of this study confirm that inpatient interdisciplinary treatment of
2 CRPS patients improves disease activity, pain, physical function, emotional function, and
3 social participation. Most improvements were maintained for up six months after discharge.
4 The majority of patients reported that their overall condition had improved during the study
5 period.

7 **KEYWORDS**

- 8 Complex regional pain syndrome
- 9 inpatient treatment
- 10 multidisciplinary
- 11 interdisciplinary
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1 INTRODUCTION

2 Complex regional pain syndrome (CRPS) is a debilitating and often chronic condition that
3 can result in significant physical, psychological, and financial burden on individuals and their
4 families ¹. The condition is characterized by a range of symptoms, including pain, sensory
5 disturbances, and motor dysfunction, and is typically triggered by trauma or surgery to a distal
6 extremity ².

7 While some patients experience benign courses, many patients develop a chronic condition
8 with persisting symptoms that can last beyond one year ^{3,4}. This results in high healthcare
9 costs and substantial absenteeism from work, imposing a significant economic burden on
10 affected individuals and society at large ⁵⁻⁷. A recent retrospective study conducted in
11 Switzerland analysed the direct healthcare costs and work incapacity associated with CRPS.
12 Within the first 5 years after the accident, insurance and treatment costs were 19 and 13 times
13 higher, respectively, compared to accidents without CRPS. Two years after the accident,
14 patients with CRPS lost 20 times more days of work (330, 7 days; mean, SD) than patients
15 without CRPS (16.1, 0.1 days; mean, SD). In two-thirds of all CRPS cases, long-term
16 disability lasting more than 90 days developed. Therefore, there is a clear need for effective
17 and evidence-based treatments for patients with persistent CRPS. However, due to the
18 complexity of the disorder, treating it effectively can be challenging. Current therapy is
19 symptom-based and involves various pharmacological, interventional, physiotherapeutic,
20 occupational, and psychiatric treatments ¹. Treatment is primarily provided in an outpatient
21 setting, but in cases where outpatient treatment options have been exhausted, inpatient
22 treatment options have been shown to be effective in improving function, activity, and social
23 participation ⁸⁻¹³. However, the benefits of inpatient treatment in terms of reducing disease
24 activity have not been investigated. Therefore, the objective of this study was to evaluate the
25 benefit of inpatient treatment in reducing disease activity in patients with CRPS who have
26 exhausted outpatient options, assessed at discharge, three-month and six-month post-

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1 discharge. Furthermore, the study sought to identify patient-related outcome variables that
2 predict a reduction in disease activity.

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1 1 **METHODS**

2 2 *Setting and recruitment of study participants*

3 3 This study was a prospective, observational, single-center cohort study conducted at the
4 4 Balgrist University Hospital in Switzerland, a privately-funded, non-profit hospital, from
5 5 September 2018 to December 2021. Participants were consecutively recruited from the
6 6 outpatient clinic of the Department of Physical Medicine & Rheumatology, with all patients
7 7 admitted for an inpatient program considered for inclusion. Potential participants were
8 8 informed about the study prior to their attendance at a pre-admission clinic, where eligibility
9 9 criteria were applied and written informed consent was obtained. The screening visit with
10 10 potential participants was performed by FB. Patients who opted not to participate in the study
11 11 still had the opportunity to attend the inpatient interdisciplinary program.

12 12 The participants in this study were assessed at admission, discharge, three-month and six-
13 13 month post-discharge. The evaluations comprised various measures of outcomes, such as
14 14 patient-reported questionnaires, clinician-reported outcomes, and a clinical assessment of
15 15 presenting signs of CRPS.

16 16 The study was approved by the Ethics Committee of Zurich (application BASEC no. 2018-
17 17 00601), and was reported in line with the STROBE reporting guidelines ¹⁴.

18 18 *Inclusion criteria*

19 19 The inclusion criteria involved adults (age ≥ 18 years) who met the Budapest criteria ¹⁵ for
20 20 CRPS in the hand or foot and had a history of unsuccessful pharmacological, physiotherapy,
21 21 or occupational therapy interventions for at least 6 months.
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23 23 *Exclusion criteria*

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3 1 Subjects with unconfirmed diagnosis, absence of consent, who lacked proficiency in the
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5 2 German language and individuals with severe mental health disorders (e.g. major depression,
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7 3 schizophrenia) were excluded from the study.
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11 5 *Description of the treatment program*

12 6 The treatment program for the patient cohort was partially standardized to allow for
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14 7 individual preferences. The patients were hospitalized for two to three weeks and received
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16 8 interdisciplinary treatment involving various disciplines. A multidisciplinary assessment was
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18 9 conducted upon admission by a physician specialized in rehabilitation medicine,
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20 10 physiotherapist, occupational therapist, and psychologist. Based on the results of the entrance
21
22 11 examinations, an individual treatment program was created, which included individual daily
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24 12 physical therapy (pacing, graded exposure, graded motor imagery, mirror therapy, pain
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26 13 education), individual occupational therapy (reintegration into daily activities, working out
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28 14 weekly/daily structures, desensitization techniques), group pool therapy and group relaxation
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30 15 training, twice-weekly individual psychological treatment (coping strategies, improving
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32 16 awareness of the affected limb, medical hypnosis), medical management (coordination of the
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34 17 interdisciplinary setting, continuous review of progress, adjustment of therapy as needed) and
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36 18 nursing (comprehensive patient care, monitoring vital signs, medication administration).
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38 19 Daily medical rounds were conducted to review the progress of each patient and drug
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40 20 treatment, which was adjusted as needed, and a grand medical round was held once a week
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42 21 with the responsible physician, nurse, physiotherapist, and social services.
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45 23 *Outcome measures*

46 24 The set of CRPS related parameters are based on the current recommendations of an
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48 25 international research consortium, which considers various aspects of the disease (Core
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50 26 Outcome Measures for complex regional PAIn syndrome Clinical Trials (COMPACT))¹⁶.

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5 2 Primary outcome measure
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8 3 The primary outcome measure was disease activity assessed using the CRPS Severity Score
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10 4 (CSS)¹⁷. The score is based on symptoms and findings of the Budapest criteria (16 items, 0 =
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12 5 not present or 1 = present, total 16 possible points). Higher scores indicate a greater severity
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14 6 of CRPS. A change of 5 or more CSS scale points reflects a clinically-significant change¹⁸.
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16 7 The CSS has been shown to possess both responsiveness and validity as an effective measure
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18 8 for assessing the severity of CRPS¹⁸.
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22 10 Assessment of secondary outcomes and further variables

23 11 *Promis-29*

24 12 The Patient Reported Outcomes Measurement Information System 29-item Health Profile
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26 13 (PROMIS-29) is designed to be used with the general population and with individuals living
27
28 14 with chronic conditions, and it assesses various aspects of health status, including depression,
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30 15 anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to
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32 16 participate in social roles and activities¹⁹. The measure consists of 28 items from seven
33
34 17 domains and a single item on pain intensity. Each item has five response options, except for
35
36 18 the pain intensity item which has eleven response options and is measured on a visual
37
38 19 analogue scale (VAS). The scores generated by PROMIS measures are interpreted based on
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40 20 T-scores with a mean of 50 and standard deviation of 10 in a reference population²⁰. The
41
42 21 Scale ranges from 20-80. Depending on the item, a higher score indicates either a positive or
43
44 22 negative outcome. Consequently, a higher score on the depression, anxiety, fatigue, sleep or
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46 23 pain interference item is linked to increased symptoms, whereas a high score on the physical
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48 24 function and social participation item is associated with improved function. In our cohort
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50 25 study, we utilized the existing recommendation from healthmeasures.com to evaluate severity
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52 26 levels, e.g. within normal limits, mild (55-60 for pain interference, depression, anxiety,
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1 fatigue and sleep, 45-40 for social participation and activities and physical function),
2 moderate (60-70; 40-30), severe (>70; <30)) based on T-scores across various domains. The
3 clinical validity of the PROMIS questionnaire has been demonstrated across various chronic
4 conditions, such as back pain ²¹.

5 6 *Pain Catastrophizing Scale (PCS)*

7 The PCS is a self-report measure designed to assess catastrophic thinking related to pain
8 among adults ²². People are asked to indicate the degree to which they have certain thoughts
9 and feelings related to pain using a 0 (not at all) to 4 scale (all the time). The total score is
10 calculated, ranging from 0-52, with higher scores indicating more pain catastrophizing. Scores
11 <30 indicate a not problematic thinking and ≥ 30 represent problematic levels of catastrophic
12 thinking ²². The PCS has been found to have good validity, accurately measuring pain
13 catastrophizing in diverse populations ²².

14 15 *Short-form McGill Pain Questionnaire-2 (SF-MPQ-2)*

16 The SF-MPQ-2 captures neuropathic pain qualities using six neuropathic items ²³. Each item
17 is rated based on a 0-10 scale with higher scores indicating more neuropathic pain (range 0-
18 60). Based on the results of a Rasch analysis, the Neuropathic Qualities subscale of the SF-
19 MPQ-2 may be used as a standalone measure for neuropathic features in CRPS ²⁴.

20 21 *EuroQoL 5-dimension 5-level instrument (EQ-5D-5L)*

22 The EQ-5D-5L is a generic health-related quality of life measure that consists of two parts:
23 the descriptive system and the Visual Analogue Scale (EQ-VAS) ²⁵. The descriptive system
24 consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/
25 depression), each with five response levels, and a total of 3125 health states are defined.
26 Health states are converted into a single index 'utility' score using a scoring algorithm. The

1 EQ-VAS provides a single global rating of self-perceived health and is scored on a 0 to
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1 EQ-VAS provides a single global rating of self-perceived health and is scored on a 0 to
2 100 mm scale representing "the worst ..." and "the best health you can imagine," respectively.
3 The EQ-5D-5L has been translated and validated in multiple languages and cultural settings,
4 making it suitable for international comparisons of health-related quality of life ²⁶.

6 *Pain Self-efficacy Questionnaire (PSEQ)*

7 The PSEQ assesses the confidence people with ongoing pain have in performing activities
8 while in pain ²⁷. The questionnaire includes 10 items, and each item is rated on a 0 to 6 scale,
9 with higher scores indicating more confidence (range 0-60). An investigation specifically
10 related to CRPS is lacking; however, a systematic review identified good validity, reliability,
11 and responsiveness for patients with musculoskeletal disorders ²⁸.

13 *Medication Quantification Scale (MQS)*

14 The MQS is a questionnaire designed for individuals with chronic pain ²⁹. The MQS for a
15 drug class is calculated by multiplying the dosage level by the detriment weight, which
16 considers side effects, toxicity, drug interactions, and long-term consequences of the drug.
17 Members of the American Pain Society ranked 22 drug classes on a seven-point scale ranging
18 from no detriment (0) to extreme detriment (6) to determine the detriment weight. Adding all
19 MQS values for individual drug classes provides an overall value for the CRPS medication
20 regimen. The MQS is considered a suitable tool for the investigation of prescription practices
21 and geographic trends in medical pain management in CRPS patients. However, a conclusive
22 statement regarding the relationship between pain intensity and pain medication use cannot be
23 made ³⁰.

25 *Patient global impression of change (PGIC)*

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3 1 The PGIC is a self-reported measure that assesses a patient's overall perception of their
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5 2 treatment response or disease progression over time ³¹. It typically asks patients to rate their
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7 3 status on a 7-point scale ranging from "very much improved" to "very much worse" or a
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9 4 similar rating scale. The PGIC is often used as a complementary measure to other more
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11 5 specific outcome measures and provides valuable information on how patients perceive their
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13 6 health status or treatment outcomes. Global Rating of Change Scales have demonstrated
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15 7 strong construct validity and notable correlations with changes in EQ-5D and Pain Rating
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17 8 Scale. A standardized response mean ranging from 0.5 to 2.7 has been reported ³².
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24 10 *Statistical analysis*

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26 11 In the present study, continuous variables were summarized with means and standard
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28 12 deviations (SD), while dichotomous variables were presented as percentages of total. Patient-
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30 13 reported outcomes were treated as continuous variables and subjected to several before-and-
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32 14 after comparisons, including admission and discharge, discharge and 3 months after, and
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34 15 discharge and 6 months after. Paired t-tests were employed for normally distributed data,
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36 16 whereas the Wilcoxon test was used for non-normally distributed data. Due to the limited
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38 17 sample size, continuous data and patient related outcomes were visually inspected to confirm
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40 18 normal distribution. In addition to reporting the mean differences with a 95% confidence
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42 19 interval (CI), the effect size of the statistical tests was assessed using Cohen's d or r (rank-
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44 20 biserial correlation) for the Wilcoxon test. Effect sizes, as measured by Cohen's d, were
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46 21 interpreted as follows: values ranging from 0 to 0.2 were deemed negligible, those up to 0.5
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48 22 were categorized as small, up to 0.8 as moderate, and any value surpassing 0.8 was regarded
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50 23 as indicative of a large effect. In the context of the Wilcoxon test, effect sizes were
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52 24 categorized as follows: values equal to or exceeding 0.1 were designated as small, those
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54 25 surpassing 0.3 were considered moderate, and an effect size of 0.5 or higher was deemed
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56 26 large. P values <.05 were considered as statistically significant.
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5 2 Patient-specific changes were quantified using mixed models, which accounted for potential
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7 3 confounders to minimize systematic errors in inference. Numerical and score endpoints were
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9 4 modelled with linear mixed models, and the number of parameters examined in the model
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11 5 was restricted to accommodate the small sample size. Based on the findings of previous work
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13 6 from Bean et al. we decided to develop a model to investigate the effect of disease activity
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15 7 with adjustments for age, symptom duration, anxiety, and pain intensity at admission³³. The
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17 8 effects of the confounding and correction variables were interpreted, and relevance of
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19 9 potential variation of the effect of correction variables across different time points was
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23 10 assessed with likelihood ratio tests.
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28 12 All statistical analyses were carried out using R version 3.6.2, while study data was stored and
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30 13 managed using Redcap versions 6.12.1 to 6.14.1 (REDCap, Vanderbilt University, Nashville,
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32 14 TN, United States).
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1 RESULTS

2 *Sample description*

3 A sample of 30 patients fulfilled our inclusion criteria and were recruited for this study. One
4 patient opted for premature discharge for personal reasons and therefore, did not complete the
5 program. Four patients opted not to participate in the study due to the extended travel
6 distance. Consequently, a total of 25 datasets were included in the analysis.

8 *Patient characteristics at admission*

9 The sample comprised primarily of female participants (n=23, 92%) with a mean age of 49.3
10 (SD 11.2) years. The upper extremity was more frequently affected (84%) than the lower
11 extremity. Surgical interventions emerged as the most frequent precipitating factor (56%),
12 followed by fractures (28%), bruises (16%), strains (12.7%) and lacerations (4.2%). The
13 average duration of symptoms at admission was 8.5 (SD 6.5) months, with a range spanning
14 from 3 to 32 months. The average length of hospitalization was 16 days (SD 3 days).

16 *Baseline characteristics*

17 Table 1 presents the baseline characteristics of the enrolled patients. On admission, the
18 disease severity was recorded at 11.4 (SD 2.4) on the CSS scale. The average pain was 5.2 (
19 SD 2.0). The excluded group exhibited similar, non statistically significant values, with a
20 disease activity score of 11 (SD 3.5, $p>0.05$) and PROMIS-29 pain level of 5.2 (SD 2.7,
21 $p>0.05$) upon admission.

22 Analysis of the Promis-29 questionnaire revealed mild limitations in the domains of
23 depression (59.1, 6.0; mean, SD), fatigue (57.1, 9.9; mean, SD), and social skills (40.1, 6.5;
24 mean, SD). Conversely, moderate limitations were observed in pain interference (64.7, 6.9;
25 mean, SD), physical function (38.6, 5.22; mean, SD), and anxiety (60.8, 6.7; mean, SD),

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3 1 compared to the reference population^{20,34}. No sleep disturbances were observed in the
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5 2 subjects.
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9 4 [Insert table 1]
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14 6 *Outcomes at discharge, three-month and six-month post-discharge*

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16 7 The treatment outcomes are summarized in table 2.
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25 11 *Primary outcome*

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27 12 Upon discharge, disease activity decreased significantly compared to baseline (CSS -2.36
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29 13 (95% CI -3.35;-1.37), $p < 0.0001$, large effect size $d = 0.95$). No statistically significant changes
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31 14 were observed at three- and six-month follow-ups. The visual trajectory is illustrated in figure
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39 17 [Insert figure 1]
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44 19 *Secondary outcomes*

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46 20 On discharge, some evidence for an improvement was observed in the following domains of
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48 21 the Promis-29: depression (-5.05 (95%CI -7.6;-2.4), $p < 0.001$, large effect size $r = 0.69$),
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50 22 anxiety (-3.32 (95%CI -6.07;-0.57), $p = 0.02$, small effect size $d = 0.5$), physical function (1.3
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52 23 (95%CI 0.2;3.05), $p = 0.03$, moderate effect size $r = 0.45$), Pain interference (-2.27 (95%CI -
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54 24 4.56;0.03), $p = 0.05$, small effect size $d = 0.61$), pain intensity (-0.88 (95%CI -1.46;-0.29),
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56 25 $p = 0.0053$, moderate effect size $d = 0.41$), fatigue (-4.63 (95%CI -7.34;-1.93), $p = 0.0018$,
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58 26 moderate effect size $d = 0.71$), and social participation (1.93 (95%CI -0.02;3.89), $p = 0.05$, small

1 effect size $d=0.41$). These improvements persisted throughout the subsequent three- and six-
2 month follow-up periods.

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4 There were no statistically significant changes observed in pain catastrophizing, pain self
5 efficacy or neuropathic pain.

6 We observed an improved quality of life on the Eq5d5l (0.06 (95%CI 0;0.12), $p=0.04$, small
7 effect size $d=0.4$) at discharge, which was sustained at three- and six-month follow-ups.

8 There was no evidence for alteration in the quantity of medication administered during the
9 inpatient stay. However, during the period between discharge and three months after, and also
10 between discharge and six months after, there was a statistically significant reduction in
11 medication usage, indicated by MQS values of -8.22 (95%CI -13.23; -3.21, $p=0.0024$, large
12 effect size $r=0.56$) and -8.69 (95%CI -13.51-3.87, $p=0.0011$, large effect size, $r=0.62$),
13 respectively.

14 15 *Patient Global Impression of Change (PGIC)*

16 On discharge 23 of 25 patients (92%) reported improvement in their overall condition. Three-
17 month and six-month post-discharge 15 of 25 (60%) respectively 14 of 24 (58%) of the
18 patients still reported further improvement in their overall condition when compared to
19 discharge. The patient global impression of change is depicted in figure 2.

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21 [Insert figure 2]

22 23 *Course of CRPS symptoms adjusted for potential confounders*

24 In the linear mixed effect model (Table 3) similar changes of CSS were calculated as in the
25 unadjusted comparisons (admission to discharge -2.22 (95%CI -3.37;-1.06), $p<0.001$).

26 Consequently, CSS effects apply, regardless of confounding and adjustment factors. Patients

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3 1 who experienced greater pain at admission (+0.76 CSS per +1 pain (95%CI 0.25;1.28),
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5 2 p=0.0038) showed increased disease activity. No association was detected between CSS and
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7 3 symptom duration, anxiety at admission and age. Similarly, no variation in association
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9 4 between CSS and pain or anxiety was observed at different timepoints.
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1 DISCUSSION

2 The aim of this study was to evaluate the benefit of inpatient treatment in reducing disease
3 activity in patients with CRPS who have exhausted outpatient options, assessed at discharge,
4 and at three-month and six-month post-discharge. The results of our study revealed a
5 reduction in disease activity from admission to discharge, a trend that persisted during the
6 three- and six-month follow-up assessments. Linear mixed models confirmed the findings of
7 the unadjusted comparisons. Additionally, a relationship between pain intensity upon
8 admission and disease activity was established.

10 RESULTS IN THE LIGHT OF THE EXISTING LITERATURE

11 Due to the complexity and the multifaceted nature of CRPS, the therapy remains a challenge
12 and no causal therapy is available ^{3,8-11,35}. In the past, several studies showed that a
13 interdisciplinary inpatient treatment is effective in improving CRPS symptoms ^{9,10,12}. The
14 main outcome measure of these studies was a reduction of pain on the numeric rating scale.
15 Additional parameters included physical function measured by range of motion and grip
16 strength of the affected hand ⁹, body perception disturbance and emotional function ¹⁰ and
17 perception and management of pain ¹². Multidisciplinary outpatient treatment programs also
18 focused on pain reduction ^{8,11}, physical function ^{8,11,13} and psychological factors such as
19 depression, anxiety and pain acceptance ^{8,11,13}. To harmonize the outcome measures of clinical
20 studies, an international committee has developed and validated the CRPS severity score
21 (CSS) ^{36,37}. Elomaa et al. have used a similar CRPS symptom count for their inpatient study
22 before CSS was developed, and showed that motor, trophic and sensory symptoms improved.
23 So far, only one study used the CSS as main outcome parameter ³, however this study
24 assessed the disease course of outpatients with no specific or predefined treatment regime.

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3 1 The present study is the first to show that inpatient treatment is able to reduce disease activity
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5 2 as assessed by CSS. We observed a significant reduction in disease activity from admission to
6
7 3 discharge, averaging -2.36 points on the CSS. In Bean et al. 2016, CSS in patients with recent
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9 4 diagnosis of CRPS (< 12 weeks) showed the greatest reductions in disease activity during the
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11 5 first six months of outpatient treatment. In this study, the mean of the baseline CSS score was
12
13 6 12.6 (SD 2.0) and thus slightly higher than in our work (mean 11.4, SD 2.4). The patients in
14
15 7 our study were admitted to inpatient treatment only after a mean symptom duration of 8.5
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17 8 months when outpatient treatment options were exhausted. The fact that we observed a
18
19 9 reduction in disease activity during hospitalization suggests that inpatient treatment is
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21 10 effective in patients with stagnant activity in longstanding disease. It is important to mention
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23 11 that the change in CSS observed in our study does not meet the threshold for clinical
24
25 12 significance of > 4.9 points on CSS as suggested by Harden et al. 2017¹⁸. This threshold was
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27 13 calculated based on the comparison of disease course in patients with more recent diagnosis
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29 14 of CRPS and newly initiated treatment to patients with longer disease duration on stable
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31 15 treatment regimes, and should reflect the smallest real difference under the assumption that
32
33 16 the stable treatment group showed no clinically relevant change in disease activity. However,
34
35 17 it should be noted that this threshold has not been externally validated. Since the patients in
36
37 18 our study reported a significant and lasting improvement in physical function, emotional
38
39 19 wellbeing and participation in activities of daily life, we suspect that a reduction in CSS < 4.9
40
41 20 points might correspond to a clinically relevant improvement. Alternatively, the CSS score
42
43 21 might be more appropriate to detect longer-term changes in disease activity as assessed by
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45 22 Harden et al. 2017¹⁸ and Bean et al. 2016³ (3 and 6 months) than the benefit of shorter
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47 23 interventions such as inpatient treatment programs.
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57 25 While the duration of therapy had no influence on pain reduction in the study by Kotsougiani-
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59 26 Fischer et al., Raqué et al. were able to demonstrate that patients receiving therapy early

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2 1 experienced better pain reduction than patients with longstanding disease (symptom duration
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4 2 < 12 months and > 24 months respectively). In our study, we found no correlation of change
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6 3 in CSS with symptom duration. However, our study included only very few patients with
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8 4 symptom duration of > 24 months.
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13 6 We observed improvements in psychological functioning, particularly in depressive
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15 7 symptoms, anxiety, and fatigue. This is in line with some previous studies ^{3,11}, while two
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17 8 studies reported no significant reductions in anxiety or emotional wellbeing ^{8,13}. In a
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19 9 prospective study by Bean et al. 2015, patients with less pain-related and general anxiety had
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21 10 less disability and pain ³³. De Jong et al. also found an association between pain-related
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23 11 anxiety and function of the affected limb ³⁸. It has been suggested that anxiety is linked to an
24
25 12 increased inflammatory state ³⁹ and sympathetic activity, which are both implicated in the
26
27 13 development of CRPS ⁴⁰. In contrast to these results, we detected no association between
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29 14 anxiety and disease activity. However, we did not assess pain-related anxiety specifically.
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33 16 Similar to McCormick et al. 2015, we found no significant decrease in medication use during
34
35 17 the treatment program. Two factors contribute to the constancy of medication use between the
36
37 18 initial assessment and discharge. Firstly, some patients experienced severe pain that persisted
38
39 19 despite exhausting their current medication dosage, necessitating a switch to alternative
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41 20 medication classes during their inpatient stay. Secondly, some patients had previously
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43 21 avoided using the affected limb due to pain and required analgesics to enable their active
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45 22 participation in the intensive physiotherapy and occupational therapy program. Like
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47 23 McCormick et al., we found a reduction in medication use in at the follow up examinations,
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49 24 indicating the success of the therapy.
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60 26 STRENGTH AND LIMITATIONS

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3 1 Our study has several strengths. In addition to individual complaints occurring in the context
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5 2 of CRPS, such as pain or functional limitations, we documented the overall health of the
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7 3 patients by means of different domains described in the methods section according to
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9 4 COMPACT¹⁶. This allows to more adequately capture the multi-layered nature of the
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11 5 disease. Furthermore, by reducing the heterogeneity of the documented parameters, a
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13 6 comparison with future studies should be simplified, and thereby lead to better evidence for
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15 7 the investigation of this rare disease. To the best of our knowledge, this study is the first to
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17 8 investigate the long-term effectiveness of a multi-modal inpatient therapy with consideration
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19 9 of the above-mentioned parameters.
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25 11 Since the data for this study were collected prospectively and the patients were included
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27 12 according to established diagnostic criteria, sampling biases, such as misdiagnosed patients,
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29 13 are reduced.
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34 15 However, it's important to acknowledge some limitations. The severity thresholds used for the
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36 16 PROMIS-29 questionnaire have been established for rheumatoid conditions and cancer.
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38 17 Therefore, despite similarities with CRPS patients, these values should be interpreted with
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40 18 caution within the context of our cohort study. Secondly, the lack of randomization and
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42 19 control group is considered a weakness of this study. Furthermore, due to the small sample
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44 20 size the generalizability of the results is limited. Finally, our study does not allow specific
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46 21 assessments of individual treatment modalities, since treatments are considered in
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48 22 combination in the form of an interdisciplinary therapy.
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53 24 IMPLICATION FOR RESEARCH

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55 25 In order to accurately assess the effectiveness of inpatient treatment for CRPS patients and
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57 26 determine the appropriate patient groups for therapy, randomized controlled trials with a large
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2 1 sample size are necessary. While this study contributes to the existing evidence supporting
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4 2 clinical, evidence-based inpatient therapy for select cases, it cannot provide definitive
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6 3 recommendations for an optimal combination of treatment options that cater to all CRPS
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8 4 patients. Further research is required to enhance our understanding of the disease's underlying
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10 5 mechanisms and to investigate the efficacy and dosages of individual modalities in relation to
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12 6 CRPS.
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18 8 **CONCLUSIONS**

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20 9 Inpatient interdisciplinary treatment for CRPS patients who have exhausted outpatient options
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22 10 shows promising improvements in disease activity, pain, physical function, depression,
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24 11 anxiety, fatigue, and social participation. However, further studies, preferably controlled,
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26 12 multicenter, or randomized controlled trials, are needed to validate the effectiveness of this
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28 13 approach and investigate potential advantages of inpatient therapy or day hospital programs
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30 14 over outpatient care. These studies would contribute to a better understanding of optimal
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32 15 treatment strategies for CRPS patients.
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2 No funding was received for this study.

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4 **CONFLICT OF INTEREST**

5 The authors declare that they have no competing interests.

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1 **FIGURE LEGENDS**

2 **Figure 1: CRPS Severity Score Boxplot**

3 **Figure 2: Patients global impression of change**

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Table 1: Descriptive statistics at admission and discharge

Domain	Admission	Discharge	
	Mean (SD)	Mean (SD)	Scale*
CSS	11.4 (2.4)	9.04 (3.03)	1-16
Promis-29			
Pain on VAS (last 7 days)	5.2 (2.0)	4.5 (2.2)	1-10
Physical function	38.6 (5.2)	40.3 (5.1)	80-20
Anxiety	60.8 (6.7)	57.6 (7.8)	20-80
Depression	59.1 (6.9)	54.4 (8.4)	20-80
Fatigue	57.1 (9.9)	52.5 (9.4)	20-80
Sleep disturbance	54.7 (4.9)	53.9 (4.6)	20-80
Pain interference	64.7 (6.-9)	62.6 (5.2)	20-80
Social participation	40.1 (6.5)	41.8 (6.1)	80-20
PCS	19.0 (10.41)	17.6 (11.8)	0-52
SF-MPQ-2	34.7 (39.3)	32.5 (41)	0-60
EQ-5D-5L	0.6 (0.2)	0.7 (0.2)	0-1
EQ-5D-5L VAS	58.5 (25.6)	54 (21.9)	0-100
PSEQ	23.8 (14.1)	27.1 (12.9)	0-60
MQS	15.3 (13.6)	13 (12.1)	

Abbreviations: CSS=CRPS Severity Score; Eq5d5l = 5 Level 5 Dimensions Euroquol
 Questionnaire; EqVAS= Eq Visual Analogue Scale; MQS=Medication Quantification Scale;
 PCS=Pain Catastrophizing Scale; Promis -29 = Patient Reported Outcomes Measurement
 Information System-29 item; PSEQ=Pain Self Efficacy Questionnaire; SD Standard
 deviation; SF-MPQ-2= short form McGill Pain Questionnaire 2; VAS=Visual Analogue Scale
 (pain)

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3 * Higher scores are associated with more symptoms, with the exception of EQ-5D-5L,
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5 PROMIS-29 physical function and social participation where lower scores are associated with
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Table 2: Outcomes at discharge, three-month and six-month post-discharge

Domain	Admission to discharge				Discharge to 3 months				Discharge to 6 months			
	Estimate	95%-CI	p-value	Effect Size (d/r)	Estimate	95%-CI	p-value	Effect Size (d/r)	Estimate	95%-CI	p-value	Effect Size (d/r)
CSS ^t	-2.36	-3.35; -1.37	< 0.0001 ***	0.95 ^d	-0.64	-1.61; 0.33	0.19	0.26 ^d	-0.56	-1.72; 0.6	0.33	0.19 ^d
PROMIS-29												
Pain on VAS ^t	-0.88	-1.46; -0.29	0.0053 **	0.61 ^d	0.39	-0.09; 0.87	0.11	0.34 ^d	0.48	-0.33; 1.29	0.24	0.25 ^d
Physical function ^w	1.30	0.20; 3.05	0.03 *	0.45 ^r	-0.04	-1.67; 1.59	0.96	0.02 ^r	0.50	-1.31; 2.32	0.57	0.07 ^r
Anxiety ^t	-3.32	-6.07; -0.57	0.02 *	0.5 ^d	-1.23	-4.64; 2.17	0.46	0.15 ^d	1.20	-2.80; 5.19	0.54	0.13 ^d
Depression ^w	-5.05	-7.60; -2.40	< 0.001 ***	0.69 ^r	1.42	-1.21; 4.04	0.28	0.3 ^r	2.50	-1.52; 6.52	0.21	0.23 ^r
Fatigue ^t	-4.63	-7.34; -1.93	0.0018 **	0.71 ^d	0.62	-3.19; 4.43	0.74	0.07 ^d	3.09	-1.96; 8.14	0.22	0.26 ^d
Sleep ^t	-1.06	-2.91; 0.79	0.25	0.24 ^d	0.25	-1.90; 2.40	0.81	0.05 ^d	2.38	0.85; 3.95	0.0084 **	0.5 ^d
Pain interference ^t	-2.27	-4.56; 0.03	0.05 *	0.41 ^d	0.36	-1.22; 1.94	0.64	0.09 ^d	0.16	-1.94; 2.25	0.88	0.03 ^d

Social Participation ^t	1.93	-0.02; 3.89	0.05*	0.41 ^d	1.72	0.20; 3.24	0.03*	0.46 ^d	1.75	-0.70; 3.95	0.19	0.32 ^d
PCS ^t	-1.36	-3.99; 1.27	0.30	0.21 ^d	-0.48	-4.15; 3.19	0.79	0.05 ^d	-2.04	-5.73; 1.65	0.26	0.23 ^d
SF-MPQ-2 ^t	-2.20	-5.69; 1.29	0.21	0.25 ^d	0.36	-4.37; 5.09	0.88	0.03 ^d	4.08	-6.08; 14.25	0.41	0.16 ^d
Eq5d5l ^t	0.06	0; 0.12	0.04*	0.41 ^d	0.03	-0.04; 0.10	0.44	0.15 ^d	-0.03	-0.13; 0.07	0.49	0.14 ^d
EqVAS ^t	-4.56	-12.25; 3.13	0.23	0.24 ^d	-3.60	-13.23; 6.03	0.45	0.15 ^d	-0.29	-11.53; 10.95	0.96	0.01 ^d
PSEQ ^t	3.28	-0.67; 7.23	0.1	0.33 ^d	0.44	-2.26; 3.14	0.74	0.07 ^d	-1.5	-5.5; 2.50	0.35	0.17 ^d
MQS ^w	-1.75	-4; 3.90	0.4	0.18 ^r	-8.22	-13.23; - 3.21	0.0024**	0.56 ^r	-8.69	-13.51; -3.87	0.0011**	0.62 ^r

* p-value <0.05 ; ** p-value <0.01; *** p-value <0.001

Abbreviations: CSS=CRPS Severity Score; Eq5d5l = 5 Level 5 Dimensions Euroqol Questionnaire; EqVAS= Eq Visual Analogue Scale;

MQS=Medication Quantification Scale; PCS=Pain Catastrophizing Scale; Promis -29 = Patient Reported Outcomes Measurement Information

System-29 item; PSEQ=Pain Self Efficacy Questionnaire; SF-MPQ-2= short form McGill Pain Questionnaire 2

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The difference (t for t-test or w for Wilcoxon test) with 95% confidence interval (CI), the p-value and the effect size (d for Cohen's D or r for Wilcoxon test) for all three comparisons between admission and discharge, between discharge and the three-month control, and between discharge and the six-month control are shown for all domains.

Table 3: Multivariate analysis of symptom severity after inpatient treatment up until six months follow-up

	CRPS Severity Score		
	Estimate ¹	95% CI	p-value
Age	-0.05	-0.15;0.04	0.3
Symptom duration	0.08	-0.06;0.23	0.28
Anxiety (Promis-29) ²	-0.15	-0.17;0.14	0.88
Pain intensity (Promis-29) ²	0.76	0.25;1.28	0.0038**
Admission to Discharge ³	-2.22	-3.37; -1.06	<0.001***
Discharge to 3 months ³	0.7	-0.46; 1.85	0.24
Discharge to 6 months ³	0.74	-0.41; 1.89	0.21

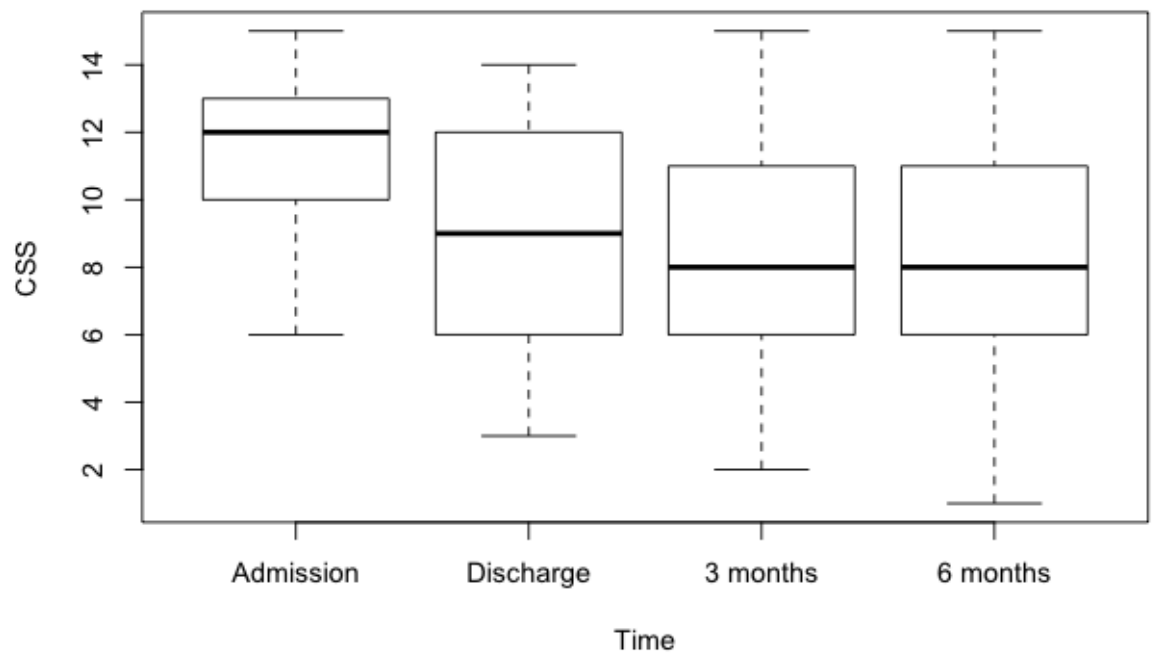
** p-value <0.01; *** p-value <0.001

¹ Comparison of outcome between admission, 3 months and 6 months compared to discharge with adjustment for age, symptom duration, anxiety and pain.

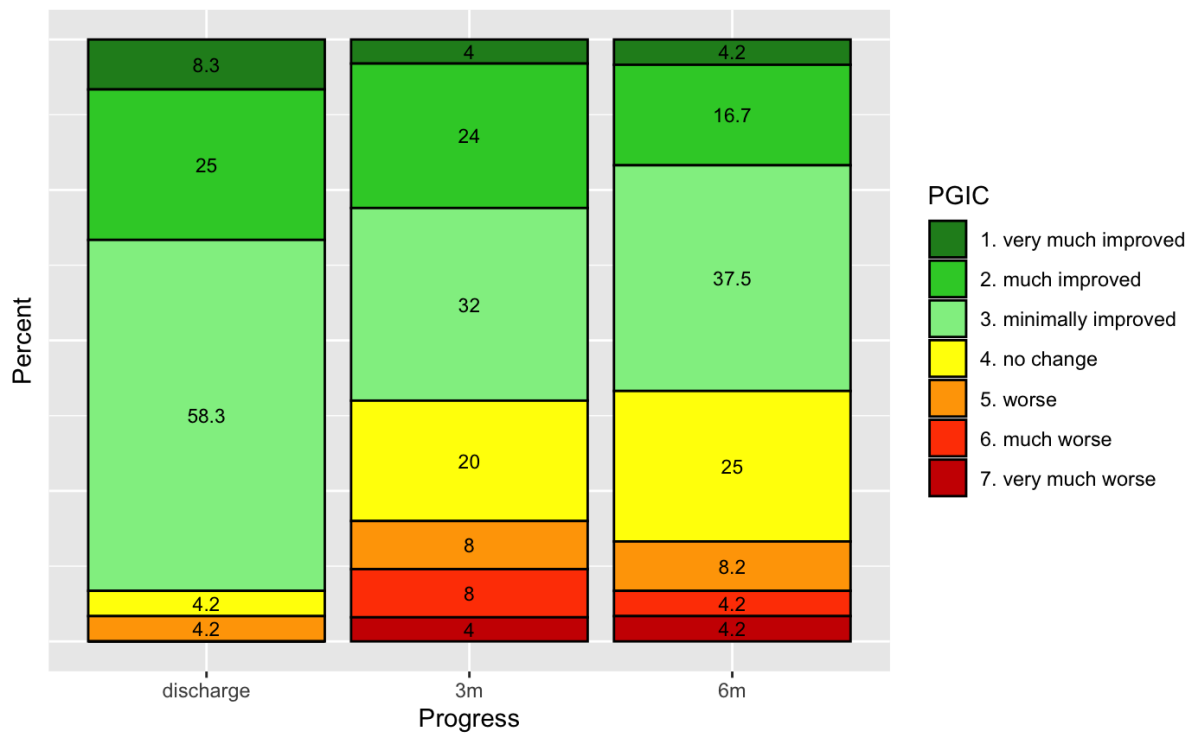
² Pain intensity and Anxiety assessed at Admission (Baseline)

³ Course of disease activity at different times after adjustment of the above-mentioned variables

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