



The role of mood in complex regional pain syndrome: Cause or consequence?

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■ MAIN POINTS

- Anxiety and depression often accompany complex regional pain syndrome.
- It's unclear if this condition precedes or follows the disease.
- The study's results indicate that mood changes stem from the disease.

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■ ABSTRACT

Aim: Complex Regional Pain Syndrome (CRPS) involves pain and dysfunction in multiple nervous system pathways. Psychological symptoms such as anxiety, depression, and difficulty coping often accompany the physical aspects of the condition. This study sought to examine whether mood-related factors play a causal role in the onset of CRPS or if individuals with pre-existing psychological conditions exhibit increased susceptibility to its development.

Materials and Methods: This is a cross-sectional study that included 131 patients with a history of trauma or surgery who were referred for rehabilitation within the first three months following the incident. Among them, 70 patients were diagnosed with CRPS, while 61 patients formed the control group. Each participant underwent evaluation through the Short Form-36, Visual Analog Scale (VAS), Beck Depression Inventory, and the Beck Anxiety Inventory.

Results: The study included 62 men and 69 women, with no significant differences in anxiety and depression scores observed between the CRPS group and the control group ($p > 0.05$ for both). However, individuals with CRPS reported notably higher scores on the VAS ($p < 0.05$). In addition, their scores were significantly lower in the Short Form-36 subdomains related to pain intensity ($p < 0.05$), social functioning ($p < 0.05$), and physical role limitations ($p < 0.05$).

Conclusion: The results indicate that an individual's baseline mood does not seem to contribute to the development of CRPS. These mood changes may be only the result of the disease, as pain level, social function, and physical role were determined to be worse in these patients.

Keywords: Anxiety, Complex regional pain syndrome, Depression, Mood, Reflex sympathetic dystrophy

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■ INTRODUCTION

Complex Regional Pain Syndrome (CRPS-I) typically emerges following an injurious event and is characterized by pain, edema, dysregulated cutaneous perfusion, and abnormal sudomotor activity [1]. CRPS frequently affects the upper or lower limbs and presents with a constellation of autonomic, sensory, and vasomotor abnormalities. Common clinical features include ongoing pain, changes in skin coloration and temperature, motor impairment, hypersensitivity, muscular and osseous wasting, excessive perspiration, and atypical patterns in hair and nail development [2].

The disease was reported to affect 13.6 individuals per 100,000 each year. It exhibits a higher prevalence in women and predominantly involves the upper limbs, often presenting with comorbidities distinct from those commonly seen in

other chronic musculoskeletal conditions [3]. The diagnosis relies on the internationally endorsed Budapest criteria [4].

Beyond its physical manifestations, CRPS is strongly linked to psychological and emotional disturbances. Affected individuals commonly experience depression, anxiety, frustration, and difficulty coping factors that can heighten pain perception and impair daily functioning [5]. These emotional disturbances may not only be consequences of chronic pain but could also influence autonomic responses and central pain processing, potentially perpetuating the condition. Psychiatric comorbidities, such as mood disorders and somatic symptom presentations, are frequently observed in this population and may compromise therapeutic outcomes. However, it is not certain whether these psychological symptoms predate the onset of CRPS or develop as a result of the disease

and its disabling effects [6].

The literature reflects ongoing debate regarding the temporal relationship between mood disorders and CRPS. Some evidence suggests that pre-existing psychological vulnerabilities such as catastrophic thinking, high anxiety levels, or poor stress resilience may contribute to disease onset [7]. Conversely, other research proposes that psychiatric symptoms arise in response to the intense pain, limited mobility, and delayed recognition often associated with CRPS. Recent findings indicate a notable rise in psychological distress following diagnosis, particularly in patients with severe or persistent symptoms [8]. While the biopsychosocial framework is widely accepted as foundational for CRPS management, the precise influence of mental health variables on both disease development and progression remains insufficiently defined and continues to be a major area of investigation [7].

This study aims to examine the influence and predictive value of mood disturbances specifically anxiety and depression in individuals diagnosed with CRPS. By assessing whether these conditions precede or result from the syndrome in outpatient contexts, the research seeks to clarify the chronological and causal interplay between psychological distress and CRPS symptoms. Elucidating these dynamics may guide the development of holistic treatment strategies and targeted screening protocols, ultimately improving clinical outcomes by integrating physical and psychological approaches.

■ MATERIALS AND METHODS

This is a cross-sectional cohort study. Ethical approval was secured from the Institutional Review Board of Baskent University Hospital (Approval No: E-94603339-604.01-484842, dated 23.07.25). All participants provided written informed consent regarding participation and the use of their data. The study adhered to the ethical standards outlined in the Declaration of Helsinki.

Patient selection and sampling

Patients referred to the physiotherapy clinic between February 2023 and February 2025, following initial evaluation by the Department of Orthopedics and Traumatology for trauma-related conditions or postoperative care, were recruited for this study. An a priori power analysis was conducted using G*Power (version 3.1.9.4). Based on a medium effect size ($d = 0.5$) consistent with previous literature [7], a minimum of 51 participants per group (total $N = 102$) was required to achieve 80% statistical power at an alpha level of 0.05.

Inclusion and exclusion criteria

Participants who suffered from trauma or undergone surgical procedures were recruited within a three-month timeframe were evaluated for inclusion to the study. Individuals diagnosed with CRPS Type I based on the Budapest criteria were assigned to the CRPS group, while those exhibiting no clinical

signs of CRPS were allocated to the control group. The primary objective of this study is to examine whether mood disturbances, such as anxiety and depression, predated the onset of complex regional pain syndrome or if they manifested subsequently as a consequence of the disease. Accordingly, only patients within the initial three months of the acute phase were included in the study cohort, given that in chronic cases, prolonged disease progression may render mood alterations an anticipated outcome.

Exclusion criteria included individuals under 18 or over 65 years of age, those with rheumatologic conditions, motor deficits, or myelopathy affecting the involved limb. Additionally, patients who had received injections, manual therapy, or physiotherapy in the affected area within the preceding three months; pregnant individuals; those demonstrating non-adherence to the treatment protocol; individuals with cognitive impairment; and those who were not willing to participate were excluded from the study cohort.

Evaluation of the participants

All assessments were conducted by a single experienced physiatrist to ensure consistency. Demographic characteristics were documented for each participant, and all individuals were instructed to accurately complete the following standardized instruments: the Visual Analog Scale (VAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and the Short Form-36 (SF-36) Health Survey.

The Visual Analog Scale is a straightforward, widely utilized tool designed to quantify subjective pain intensity. It involves a 10-centimeter horizontal or vertical line anchored by descriptors at each end (0 indicating "no pain" and 10 indicating "the most severe pain"). Participants mark the point that best reflects their current pain intensity, and the distance from the "no pain" endpoint to the marked location is measured in centimeters or millimeters. The VAS is recognized for its simplicity, reproducibility, and minimal equipment requirements, and it has been validated as a reliable measure for both acute and chronic pain [9].

The Beck Anxiety Inventory is a self-report questionnaire designed to assess the frequency of anxiety symptoms using a 4-point Likert scale. Responses range from 0 ("not at all") to 3 ("severely"), with total scores spanning 0 to 63. Higher scores denote greater levels of anxiety. Turkish version of the BAI was validated by Ulusoy et al., making it suitable for clinical and research use in Turkish populations [10].

The Beck Depression Inventory consists of 21 items assessing various emotional and somatic symptoms of depression. Each item offers four graded response options, reflecting symptom severity. Participants are instructed to select responses that best represent their emotional state. Total scores are interpreted as follows: 0–9 indicates no depression; 10–18 suggests mild depression; 19–29 corresponds to moderate depression; and 30–63 indicates a high likelihood of severe de-

Table 1. Demographic characteristics of the participants.

		CPRS Group (n= 70)	Control Group (n= 61)
Age (mean ± SD)		46.51±13.57	42.24±14.60
		n (%)	n (%)
Gender	Female	39 (55.7)	30 (49.2)
	Male	31 (44.3)	31 (50.8)
Education	Illiterate	2 (2.9)	1 (1.6)
	Primary school	36 (51.4)	29 (47.5)
	Secondary school	12 (17.1)	8 (13.1)
	High school	9 (12.9)	13 (21.3)
	University	11 (15.7)	10 (16.4)
Occupation	Unemployed	2 (2.9)	0 (0)
	Worker	16 (22.9)	11 (18)
	Retired	8 (11.4)	7 (7)
	Desc worker	14 (20)	18 (29.5)
	Housewife	28 (40)	20 (32.8)
	Student	2 (2.9)	5 (8.2)
Localization	Upper extremity	42 (60)	0 (0)
	Lower extremity	28 (40)	0 (0)
Operation history		23 (32.8)	14 (23.0)
Trauma history		56 (80)	11 (18)
Psychiatric disease		7 (10)	5 (8.2)

CRPS: Complex regional pain syndrome.

Table 2

Value	P value
Gender [†]	$\chi^2 = 0.058, p = 0.455$
Education [#]	0.729
Occupation [#]	0.399
Localization [#]	0.001*
Operation history [†]	$\chi^2 = 1.578, p = 0.209$
History of trauma [#]	0.001*
History of psychiatric disease [#]	0.877

[†]Pearson Chi Square test, [#]Fisher's exact test, *p < 0.05 statistically significant.

pressive symptoms. BDI has been shown to be usable across diverse populations [11].

To evaluate health-related quality of life, the SF-36 Health Survey was administered. This instrument is one of the most extensively used general health status questionnaires and has been validated for use in Turkish populations. The SF-36 assesses nine domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, emotional role limitations, mental health, and perceived changes in health over time. Higher subscale scores reflect better perceived health and well-being, while lower scores suggest diminished quality of life [12].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies (n) and percentages (%), while continuous variables were assessed

for normality using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD), whereas non-normally distributed data were summarized as median (minimum–maximum).

Due to the non-normal distribution of the data, the Mann–Whitney U test was used to compare anxiety, depression, and SF-36 scores between groups. Categorical comparisons were conducted using the Pearson chi-square (χ^2) test or Fisher's exact test. Effect sizes were calculated using the rank-biserial correlation. For all analyses, a p-value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

The study population comprised 131 individuals (62 males, 69 females). Of these, 70 patients were diagnosed with Complex Regional Pain Syndrome (CRPS), while 61 individuals constituted the control group. The mean age of the participants was 44.53±14.17 years. The majority of participants had completed primary education. Regarding occupation, a significant proportion were housewives, while a considerable segment worked in labor-intensive jobs. Among patients with CRPS, approximately 60% reported a history of trauma or surgical intervention involving the upper extremities, whereas the remaining 40% presented with involvement of the lower extremities. Specifically, 32.8% of CRPS patients had a documented history of surgery, while a substantially larger proportion (80%) reported a prior traumatic injury. The demographic and sociodemographic profiles of the participants are summarized in Table 1.

Table 3. Comparison of anxiety, depression and quality of life parameters between complex regional pain syndrome group and control group.

Valuable	Median	Min-Max	u	Effect size#	p
VAS	3	0-10	550.5	0.742	0.001*
BDI	8	0-35	1890.5	0.115	0.258
BAI	7	0-44	2016.0	-0.056	0.582
PF	80	0-100	1827.0	-0.144	0.154
PH	25	0-100	1292.0	-0.395	0.001*
EP	66.7	0-100	1875.0	-0.122	0.214
Energy/Fatigue	60	15-100	1927.0	-0.097	0.336
EW	60	16-100	1887.0	-0.116	0.251
SF	75	12.5-100	1696.0	-0.206	0.041*
Pain	62	0-100	1673.5	-0.216	0.033*
General health	62	5-100	1979.5	-0.073	0.472
Health change	50	25-75	2085.0	0.023	0.801

#Man-Witney U test, #Rank-Biserial Correlation, *p < 0.05 statistically significant. VAS: Visual Analog Score, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, PF: Physical functioning, PH: Role limitations due to physical health, EW: Emotional well-being, SF: Social function.

Comparisons of categorical variables

Comparative analysis revealed no statistically significant associations between the incidence of CRPS and gender, education level, occupation, history of surgery, or psychiatric comorbidities ($p > 0.05$). In contrast, both the localization of the pathology ($p = 0.001$) and a history of trauma ($p = 0.001$) were significantly associated with a CRPS diagnosis. The details are summarized in Table 2.

Clinical and quality of life outcomes

There were no statistically significant differences between the CRPS and control groups regarding anxiety ($p = 0.582$) or depression ($p = 0.258$) levels. However, patients with CRPS demonstrated significantly higher pain intensity according to VAS scores ($p = 0.001$). Furthermore, specific subdomains of the SF-36 health survey—specifically bodily pain ($p = 0.033$), social functioning ($p = 0.041$), and physical role limitations ($p = 0.001$)—were significantly more impaired in the CRPS group compared to controls. The remaining SF-36 subscales did not differ significantly between the groups ($p > 0.05$). Comparisons of anxiety, depression, and quality of life parameters are presented in Table 3.

DISCUSSION

In the current study, no statistically significant differences in anxiety or depression scores were observed between individuals diagnosed with CRPS and the control group. However, participants in the CRPS group reported significantly greater pain intensity, as measured by the Visual Analog Scale (VAS). Moreover, specific domains of the SF-36 survey—namely bodily pain, physical role limitations, and social functioning—were notably more impaired in the CRPS group, while the remaining subscales showed no significant between-group differences.

The mean age of patients in the CRPS cohort was 46.51 years, aligning closely with findings from Cave et al., who reported a mean age of 47.1 years in an 8-year longitudinal study [7]. Regarding anatomical distribution, 60% of CRPS patients in

this study exhibited upper extremity involvement, which is consistent with the broader literature identifying the upper limbs as the most frequently affected region [3-7]. A female predominance was observed in the CRPS group (55.7% female vs. 44.3% male), consistent with earlier studies reporting higher incidence rates among females and frequent upper extremity involvement [3-13]. One plausible explanation is that women may engage more frequently in domestic labor that predisposes them to upper limb injuries, thereby increasing the risk of developing CRPS.

A significantly higher incidence of preceding trauma was noted in the CRPS group compared to controls. While the precise pathophysiological mechanisms underlying CRPS remain debated, numerous publications identify trauma as a primary precipitating factor—a relationship clearly observed in this investigation.

The relationship between CRPS and psychological factors remains controversial. A retrospective case-control study involving 186 CRPS patients and 697 matched controls found no substantial association between CRPS and psychological conditions such as anxiety or depression [13]. Similarly, a systematic review of 31 empirical studies—most rated as having low to moderate methodological rigor—suggested that higher-quality studies generally did not identify psychological traits (e.g., anxiety, depression, neuroticism) as predictors of CRPS. However, exposure to stressful life events appeared to increase risk, warranting more rigorous investigation [14].

It is important to note that this study assessed participants within three months of their CRPS diagnosis, corresponding to the acute phase of the disease. The timing of assessment is critical, as psychiatric comorbidities often emerge or intensify with chronicity. Many studies fail to specify the interval between diagnosis and study inclusion, a methodological limitation that obscures differences between early- and late-stage CRPS and complicates assessments of treatment efficacy [13,14].

Literature on the chronic phase presents a different picture. A 2017 prospective study reported that 38% of CRPS patients

screened positive for post-traumatic stress disorder (PTSD), with most cases predating CRPS onset. This suggests PTSD may be a predisposing factor, particularly as maladaptive coping mechanisms were found to correlate with PTSD severity [15]. In another study of 50 patients, 60% had a history of depression, 20% reported panic attacks, and 18% had experienced alcohol or substance use disorders [16]. A separate retrospective analysis of 64 CRPS patients similarly documented a higher prevalence of psychological disorders—including adjustment disorders, depression, substance misuse, and personality disorders—compared to patients with other chronic pain conditions [5].

Further research indicates that while pre-CRPS psychiatric rates may mirror the general population, these rates escalate following onset [8]. For instance, one study found that post-diagnosis, the incidence of psychiatric disorders rose by 76%, suggesting a significant psychosocial impact of the disease [8]. Rommel et al. found psychiatric comorbidities in 78% of CRPS cases, with adjustment disorders and major depression being the most frequent [17]. Additionally, psychosocial evaluations indicate that CRPS contributes to adverse psychological states and is associated with diminished quality of life and occupational functioning [18].

The relationship between mood and pain may be bidirectional or cyclothymic. Tajerian et al., in an experimental study on mice, demonstrated that neuropathic pain is retained through neuroplastic mechanisms, potentially precipitating mood alterations such as anxiety [19]. Pereira et al. conducted a one-year follow-up of CRPS patients and determined that mood disturbances were diagnosed with greater frequency in this cohort compared to patients without CRPS [20]. Brinkers et al. demonstrated that psychiatric conditions can influence pain perception in CRPS and found that both neuropathic pain and psychiatric disorders responded to similar psychotropic treatments [5].

Despite this evidence, our study found no significant difference in anxiety or depression scores. This discrepancy is likely attributable to the cross-sectional design and the restriction of our sample to the acute phase (first three months), whereas mood disorders may manifest more prominently as the condition becomes chronic. Consequently, multicenter cohort studies with extended longitudinal follow-up are warranted.

Recent studies exploring the link between anxiety and CRPS suggest biological and behavioral mechanisms underlying this relationship. Anxiety may exacerbate CRPS symptoms by enhancing systemic inflammation and promoting peripheral sensitization through elevated catecholamine levels. Additionally, anxiety is associated with altered brain processing that can lead to central sensitization, amplifying the subjective pain experience. Individuals with heightened anxiety may also exhibit greater attentional bias toward pain, increasing symptom intensity through hypervigilance and catastrophic interpretation [15,16].

Regarding functional outcomes, CRPS patients in the current study reported significantly greater pain intensity on the VAS, and their physical role functioning and social participation (SF-36) were more severely compromised than in controls. Possible explanations include the effects of limb immobilization, which can lead to hyperalgesia, trophic changes, vascular dysregulation, and cortical reorganization. Cognitive and perceptual factors may also play a role; uncertainty or misunderstanding about the nature of CRPS may foster negative health beliefs and perceptions of disability, further intensifying the experience of pain and limiting functional recovery [17,18].

Limitations

This study has several limitations. First, the cross-sectional design precludes any inference of causal relationships between CRPS and associated psychological or functional outcomes. Second, reliance on self-administered instruments such as the SF-36 and VAS introduces the potential for response bias. Third, the study did not comprehensively control for confounding variables, including concurrent medication use and coexisting medical conditions. Fourth, patients were recruited from a single center within a defined time frame, which may limit generalizability.

A significant challenge in this field is recruiting patients who meet strict inclusion criteria, as CRPS is relatively uncommon. This study was powered at 80%; however, a causal analysis would require a substantially larger sample size. Additionally, our study focused exclusively on the acute phase (within three months of diagnosis) to determine if emotional difficulties existed prior to the chronic progression of the syndrome. Future research should encompass personality assessments and longitudinal follow-up of chronic cases. Finally, similar to the review by Beerthuizen et al. [21], we found no direct association between psychological factors and CRPS. However, unlike their review, our study did not examine the impact of significant life events, representing an important area for future comprehensive investigation.

CONCLUSION

Although no significant differences in anxiety and depression were observed between CRPS patients and controls in the acute phase, those affected by CRPS experienced markedly greater pain intensity. Additionally, the CRPS cohort demonstrated significant deficits in domains related to pain severity, social functioning, and physical role performance. These results highlight the profound impact of CRPS on functional abilities and overall quality of life. The absence of significant differences in other SF-36 subscales suggests that the burden of CRPS is localized to specific facets of daily living. Targeted interventions addressing these functional impairments may enhance therapeutic outcomes and inform comprehensive, multidisciplinary management strategies.

Abbreviations

Complex Regional Pain Syndrome (CRPS)

VAS: Visual Analog Scale

BDI: Beck Depression Inventory

BAI: Beck Anxiety Inventory.

SF-36: Short Form-36

PF: Physical functioning

PH: Role limitations due to physical health

EP: Role limitations due to emotional problems

F: Fatigue

EW: Emotional well-being

SF: Social functioning

P: Pain

GH: General health

HC: Health change

PTSD: Post-traumatic stress disorder

Data Availability Statement: Data cannot be shared openly to protect study participant privacy. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Ethical approval was obtained from the Baskent University Non-Interventional Clinical Research Ethics Committee (Decision No: E-94603339-604.01-484842; Date: 23.07.2025).

Informed Consent: Written informed consent was provided by all participants or their legal guardians.

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