

# Factors associated with complex regional pain syndrome type I in patients with surgically treated distal radius fracture

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## Abstract

**Purpose** Wrist fracture is considered a typical initiating trauma for complex regional pain syndrome type I (CRPS I). However, few studies have comprehensively evaluated factors associated with the occurrence of CRPS I after the surgical treatment of a distal radius fracture (DRF). This study evaluates the factors influencing the occurrence of CRPS I after the surgical treatment of a DRF.

**Methods** A total of 477 patients with a DRF who had been treated surgically were enrolled in this prospective observational study. Patients were followed for 6 months after surgery, and CRPS I was diagnosed using the Budapest diagnostic criteria for research. The factors assessed for the development of CRPS I were age, gender, the body mass index, the type of fracture, the energy of trauma, the number of trial reductions, the type of surgery, and the duration of immobilization. A multivariate logistic regression analysis was conducted to identify independent predictors of the occurrence of CRPS I.

**Results** Among the 477 patients, 42 (8.8 %) satisfied the Budapest criteria for CRPS I within 6 months of surgery. Female patients developed CRPS I more frequently, and the patients who developed CRPS I were older and more likely to sustain a high energy injury or have a comminuted fracture. According to the multivariate analysis, female patients and those with a high energy trauma or severe fracture type were significantly more likely to develop CRPS I ( $p = 0.02, 0.01, \text{ and } 0.01$ , respectively).

**Conclusions** High energy injuries, severe fractures, and the female gender contribute to the development of CRPS I after the surgical treatment of DRF. The results have important implications for physicians who wish to identify patients at high risk for CRPS I after operative fixation for DRF and instigate treatment accordingly.

**Keywords** Complex regional pain syndrome · Distal radius fracture · Surgical treatment · Risk factors

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## Introduction

Fractures of the distal radius are the most common type of fracture in the upper extremity and represent a serious public health concern [1]. Recently, there has been more aggressive fracture fixation in patients with a distal radius fracture to enable patients to resume daily activities earlier and more independently [1, 2]. On the other hand, patients with fracture in the upper extremity are at high risk for developing complex regional pain syndrome type I (CRPS I) [3, 4], with reported incidence rates after a distal radius fracture ranging from 1 to 37 % [4–9]. The occurrence of CRPS I has a serious impact on the patient's quality of life and daily function because it causes severe pain with adverse psychosocial and socioeconomic effects [10, 11].

CRPS is a challenging condition with symptoms and signs such as pain, swelling, and regional vasomotor instability, which tend to be more severe than expected for the extent and location of the initial injury [12]. Differentiated by the presence of a demonstrated nerve lesion, CRPS can be classified into type I and type II, of which type I, without a nerve lesion, is more common [11]. The pathophysiology of CRPS I has not been determined and its treatment remains largely empirical and symptom based [13]. Early identification and intensified treatment have been reported to facilitate the recovery of patients with CRPS I [14, 15].

Although several studies have identified various risk factors for CRPS I after a fracture in the upper extremity, no consensus has been reached on the relationship between demographic or medical factors and the development of CRPS I [4, 16, 17]. This study hypothesizes that the development of CRPS I after distal radius surgery may be driven by demographic or medical risk factors and thus investigates patient-, injury-, and treatment-related factors associated with the development of CRPS I in patients treated surgically for a distal radius fracture.

## Patients and methods

A total of 498 patients with a distal radius fracture treated surgically between July 2010 and April 2013 were enrolled in this study. These patients were recruited from a tertiary care university hospital serving as a regional emergency-trauma center. The institutional review board of the university approved this study, and all patients provided informed consent. The operative criteria were as follows: (1) radial shortening of  $>5$  mm, (2) dorsal angulation of  $>10^\circ$  or volar angulation of  $>20^\circ$  in wrist lateral radiographs, (3) radial inclination of  $<10^\circ$  in wrist postero-anterior view and (4) an articular step-off of  $>2$  mm. A total of 21 patients with (1) systemic, multiorgan, or head injuries, (2) concomitant wrist or upper-extremity injuries, (3) bilateral fractures, (4) treated more than 2 weeks after initial injury, or (5) less than 6 months follow-up were excluded. Table 1 shows the demographic profile of remaining 477 patients.

The patients were assessed for symptoms and signs of CRPS I by two orthopedic hand specialists 6 weeks (range 5–7), 12 weeks (11–14), or 24 weeks (24–28) after surgery. When a patient was diagnosed to have symptoms related to CRPS I by one hand specialist, the patient was referred to the other hand specialist for the diagnosis of CRPS I at each session. The patient was diagnosed to have CRPS I when the two hand surgeons agree to the diagnosis. CRPS I was diagnosed using the Budapest diagnostic criteria for research (Table 2), which is a modified criteria of

**Table 1** Demographic-, injury-, treatment-related variables associated with CRPS I in patients with surgically treated distal radius fracture

Variable	<i>n</i>	CRPS (+)	CRPS (–)	<i>p</i>
Gender				
Female	262	30	232	<b>0.02</b>
Male	215	12	203	
Age (years) <sup>a</sup>		56.9 ± 18.7	49.9 ± 21.2	<b>0.02</b>
Side of fractures				
Dominant	274	27	247	0.25
Non-dominant	203	15	188	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>		23.5 ± 6.0	23.8 ± 7.0	0.76
Fracture type (AO)				
A (extra-articular)	239	14	225	<b>0.02</b>
B (partial articular)	87	7	80	
C (complete articular)	151	21	130	
Comminuted				
+	191	25	166	<b>0.01</b>
–	286	17	269	
Articular involvement				
+	239	26	213	0.11
–	238	16	222	
Energy of injury <sup>b</sup>				
Low	422	32	390	<b>0.02</b>
High	55	10	45	
Number of trial reduction				
≤1	323	27	296	0.57
≥2	151	15	136	
Type of surgery				
OR and internal fixation	347	26	321	0.10
CR and external fixation	130	16	114	
Immobilization				
≤6 weeks	290	21	269	0.13
>6 weeks	187	21	166	

Statistically significant values are in bold

BMI body mass index, OR open reduction, CR closed reduction

<sup>a</sup> Values are expressed as mean ± standard deviation; the remaining values are expressed as number of patients

<sup>b</sup> The energy of injury was classified as low (a simple fall from a standing position) or high (any other injury including open fractures, combined muscle/tendon injuries, and car accident or industrial crushing/abrasion wounds)

the International Association for the Study of Pain (IASP, 2007) [18, 19]. In the present study, CRPS I was diagnosed when continuing pain disproportionate to the distal radius

**Table 2** Budapest diagnostic criteria for CRPS (for research purpose)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in all four following categories
Sensory: reports of hyperesthesia and/or allodynia
Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/Edema: reports of edema and/or sweating changes and/or sweating asymmetry
Motor/Trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories
Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
Vasomotor: evidence of temperature asymmetry (>1 °C) and/or skin color changes and/or asymmetry
Sudomotor/Edema: evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/Trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

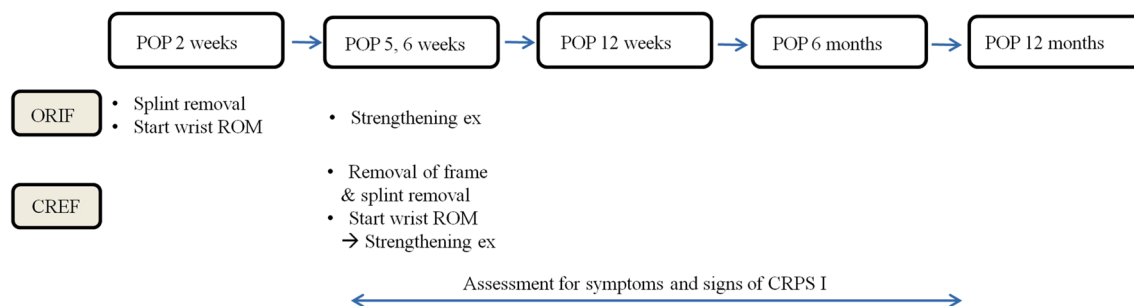
fracture was present and when four symptoms from each category and at least two signs from different categories were present in the wrist, including the area distal to the wrist (hand and fingers). These four symptom categories included (1) hyperalgesia or allodynia (sensory), (2) skin color asymmetry and temperature (vasomotor), (3) edema or sweating asymmetry (sudomotor/oedema), and (4) a decreased range of motion, motor dysfunction, or a trophic change (motor/trophic). The four sign categories included (1) evidence of hyperalgesia (pinprick) and allodynia (light touch), (2) evidence of temperature asymmetry or a skin color change, (3) evidence of edema or a sweating change, and (4) evidence of a decreased range of motion, motor dysfunction, or trophic changes.

CRPS I risk factors are multifactorial and include patient-, injury- and treatment-related factors. Based on previous studies of these factors after trauma to the upper extremity [4–6, 16, 17, 20–22], several potentially associated patient-, trauma-, and treatment-related factors are considered: patient-related factors including age, gender, and body mass index (BMI); trauma-related factors including the type of fracture (comminution or articular involvement) and the energy of trauma; and treatment-related factors including the number of trial reductions, the type of surgery, and the duration of immobilization. The energy of injury was classified as low (a simple fall from a

standing position) or high (any other injury including open fractures, combined muscle/tendon injuries, and car accident or industrial crushing/abrasion wounds). All operations were performed by two orthopedic hand surgeons with 15 and 8 years of orthopedic experience, respectively. All extra-articular (AO type A) and partial articular (AO type B) fractures were treated by open reduction and plating, and intra-articular (AO type C) fractures were treated at the surgeon's discretion. Patients undergoing volar plating were treated with a short-arm splint for 2 weeks followed by a removable short-arm brace around 2 weeks as required by the patients. Patients who underwent closed reduction and external fixation were treated with a short-arm splint for 2 weeks, and the external fixator was removed after 5 weeks from surgery, followed by a removable brace as required. Patients were advised to elevate the affected arm and perform finger range-of-motion exercises immediately after surgery. Wrist range-of-motion exercises were initiated immediately after the removal of the splint in the case of internal fixation and after the removal of the frame in the case of external fixation. Patients were instructed to perform daily activities after splint removal and to use the wrist brace as required only for physical labor using the hand. All patients had formal physiotherapy and were given a standardized home exercise program, emphasizing an active and passive range of motion and edema control of the hand/wrist. The frequency of physiotherapy was typically twice per week, although more or less frequent therapy sessions took place for some patients based on individual circumstances. Patients were followed up 2, 6 weeks, 3, 6, and 12 months after surgery by the same orthopedic hand specialist at the orthopedic outpatient clinic (Fig. 1). The patients who had been diagnosed with CRPS I at each occasion were given treatments combining oral medication and physical therapy, which was tailored to each individual person. Physical therapy interventions for CRPS I included specific modalities such as transcutaneous electrical nerve stimulation, tactile desensitization, massage, and contrast bath therapy, and oral medication included anti-inflammatories such as corticosteroid and nonsteroidal anti-inflammatory drug, antidepressant, and GABA analogs such as gabapentin and pregabalin.

#### Statistical analysis

At least 10 cases are recommended per variable in the smaller of two groups in a logistic regression analysis to reduce the likelihood of an invalid model [23]. In this present study, the number of events per predictive variable (cases per variable) in the logistic regression analysis was set to 10 to avoid a major bias. During the study design stage, a CRPS I incidence rate of 10 % was assumed for



**Fig. 1** Follow-ups in the study. The patients were assessed for symptoms and signs of CRPS I by two orthopedic hand specialists 6, 12, and 24 weeks after surgery. *ORIF* open reduction and internal fixation, *CREF* closed reduction and external fixation, *ROM* range of motion, *ex* exercise

patients with a distal radius fracture based on previous research [4, 24, 25]. Therefore, 400 patients were required (for 40 occurrences of CRPS I) to evaluate four potential predictors of CRPS I for the multiple logistic regression analysis, which were selected through a univariate regression analysis.

Descriptive statistics were used to summarize patient demographics and radiographic measurements. To detect interactions between demographic and medical variables with respect to the occurrence of CRPS I, the  $\chi^2$  test and *t* test were conducted for categorical and continuous variables, respectively. The Kolmogorov–Smirnov test was employed to identify the normality of variable distributions. Independent variables significant at the  $p < 0.1$  level were included in the multivariate regression model to prevent model overfitting. Univariate and multivariate logistic regression analyses were conducted to identify independent predictors of CRPS I development after surgery for a distal radius fracture as well as to identify confounding effects of variables. Statistical significance was accepted for  $p < 0.05$ .

## Results

Among the 477 patients, 42 (8.8 %) met the Budapest criteria for CRPS I within 6 months of surgery. The numbers of patients who were newly diagnosed with CRPS I (incidence) were 28, 14, and 0, and those who met the criteria at each occasion (prevalence) were 28, 34, and 18 at 6, 12, and 24 weeks after surgery, respectively. Of 28 patients diagnosed with CRPS I at 6 weeks, in 20 patients symptoms and signs persisted at 12 week assessment, in 8 patients resolved between 6 and 12 weeks, and in 14 patients appeared within this period. Of 34 patients who meet the criteria of CRPS I at 12 weeks, in 18 patients symptoms and signs persisted at 24 week assessment, and in 16 patients resolved between 12 and 24 weeks, and no patient appeared within this period. The mean patient age was  $50.5 \pm 19.2$  years; 262 (55 %) were female; and 274

(57 %) had a dominant side fracture. In addition, 191 fractures (40 %) were comminuted, and 239 (50 %) involved an intra-articular portion. Further, 347 (73 %) patients were treated by open reduction and internal fixation, and 151 (27 %) by closed reduction and external fixation.

According to the bivariate relationship analysis, gender, age, fracture type, and high energy injury proportions among patients with and without CRPS I showed significant differences (Table 1). More specifically, 6 % of male patients and 11 % of female patients developed CRPS I ( $p = 0.02$ ). Patients with CRPS I were older ( $p = 0.02$ ) and more likely to sustain high energy injuries and to have comminuted fractures ( $p = 0.02$  and  $0.01$ , respectively). On the other hand, no differences were found between the two groups in terms of the fracture side, the BMI, intra-articular involvement, the number of attempted reductions, and the type of surgery.

According to the logistic regression analysis, the univariate model showed that female patients, older patients, severe fractures, and high energy injuries were potential risk factors for CRPS I development in patients with a surgically treated distal radius fracture (Table 3). In the multivariate logistic analyses, female patients (aOR 2.17;

**Table 3** Univariate logistic analyses

Variables	cOR	95 % CI
Female gender	<b>1.859</b>	<b>1.214–3.408</b>
Age	<b>1.344</b>	<b>1.120–1.756</b>
Side of fracture	1.242	0.685–2.252
BMI	0.984	0.924–1.060
Fracture type	<b>2.141</b>	<b>1.237–4.034</b>
High energy trauma	<b>2.299</b>	<b>1.232–4.978</b>
Number of trial reductions	1.266	0.699–2.292
Type of surgery	1.625	0.899–2.937
Immobilization duration	1.539	0.858–2.759

Statistically significant values are in bold  
cOR crude odds ratio, CI confidence interval

95 % CI 1.49–6.03), severe type of fracture (aOR 3.12; 95 % CI 1.52–8.02) and high energy injuries (aOR 3.33; 95 % CI 1.63–10.12) contributed significantly to the development of CRPS I (Table 4).

## Discussion

Although several studies have evaluated the effects of demographic or medical factors on CRPS I development,

**Table 4** Multivariate logistic regression analyses for the prediction of CRPS I after distal radius surgery

Variables	aOR	95 % CI	<i>p</i>
Female	2.172	1.492–6.034	0.02
Fracture type	3.123	1.522–8.023	0.01
High energy trauma	3.332	1.632–10.121	0.01

aOR adjusted odds ratio, CI confidence interval

there has been no consensus because of study heterogeneity and the inclusion of different treatment methods (Table 5) [4–6, 16, 17, 20–22]. The present study demonstrates that comminuted fractures, high energy injuries, and the female gender contribute to the development of CRPS I after the surgical treatment of distal radius fractures. These identified factors are in concordance with previous findings of Zollinger et al. [5] who recruited conservatively treated patients and used the Veldman diagnostic criteria for CRPS I. The incidence of CRPS I after distal radius fractures (8.8 %) was rather higher than expected, given the diagnostic criteria used in the study. The method used to diagnose CRPS I determines the incidence of CRPS I to a large extent [4, 25], and the Budapest criteria for CRPS I has a relative high specificity (0.79) compared with the Veldman or IASP criteria [4, 26]. The relative high incidence rate in the present study might be related with the fact that we enrolled only patients with surgically treated distal radius fractures (they had more severe type of fracture than those treated conservatively) recruited from a

**Table 5** Literature review about risk factors for occurrence of CRPS I in patients with distal radius fracture

References	Study subjects	Measured variables	Findings
Roumen et al. [6]	101 conservatively or surgically treated patients	Fracture type	There was no correlation between the development of CRPS and the fracture type or anatomical end result
Bickerstaff et al. [19]	274 conservatively treated patients	Age, sex, handedness Fracture type Manipulation (or displacement)	Patients with CRPS had the more severe type and displacement of fractures
Zollinger et al. [5]	123 conservatively treated patients	Age, sex, handedness Fracture type Reduction, complaints in plasters	A higher CRPS rate in females, elderly patients, and with more comminution in the fracture In logistic regression analysis, fracture type, complaints in plaster, and vitamin C were significant predictors
Zollinger et al. [20]	416 conservatively or surgically treated patients	Sex, age, side of fracture Fracture type, dislocation Reduction, complaints in cast	Only complaint in plaster and vitamin C therapy were associated with the development of CRPS I The CRPS I was not associated with type of fractures and treatments
Demir et al. [21]	165 conservatively or surgically treated patients	Age, gender, handedness Tissue types injured	Female gender and motor nerve injury are risk factors for CRPS I
Beerthuizen et al. [4]	218 conservatively or surgically treated patients with distal radius fracture (total 596 including lower extremity)	Sex, age, handedness, education Fracture type, dislocation Type of treatment, Days in plasters	Intra-articular fracture, dislocations, musculoskeletal comorbidities were associated with the occurrence of CRPS I in patients with distal radius fracture
Current study (2014)	477 surgically treated patients	Age, gender, bone mineral density Comminution, articular involvement, energy of trauma Number of reduction trial, type of surgery, duration of immobilization	Female gender, severe type of fracture, and high energy trauma contributed to the development of CRPS I after surgical treatment of distal radius fracture

tertiary care hospital serving as a regional emergency-trauma center.

The relationship between injury severity and CRPS I development has been controversial [16]. Some studies have reported no relationship between the type of fracture and CRPS I development [21, 27, 28], whereas others have concluded CRPS I to be more common after severe fractures [4, 5, 16]. The results indicate that fracture severity was a significant predictor of CRPS I development. More specifically, the comminution of the distal radius, not the involvement of intra-articular portion, was an important predictor of CRPS I. Comminution of distal radius fracture relates with higher overall incidence of complications following surgical treatment of distal radius fractures [29]. Soft-tissue injuries or open wounds related to high energy trauma are associated with persistent pain or disability even for healed fracture [30], and the results of this study demonstrate that distal radius fractures from high energy injuries led to a 2.3-fold increase in the risk of CRPS I development. In terms of patient-related factors, the female gender has been widely believed to influence CRPS I frequency [5, 16, 22] despite some studies attributing this increased incidence to higher incidence of distal radial fracture in female patients [20]. According to the logistic regression analysis of this study, female patients were 2.2 times more likely to develop CRPS I.

Some studies have suggested that CRPS I development is more likely after external fixation than after other surgical treatment procedures [31, 32]. In the present study, external fixation was not a risk factor of CRPS I occurrence, which is consistent with previous research [33] in that external fixation does not necessarily lead to a higher incidence of CRPS I. The high incidence of CRPS I after external fixation found in previous research might be related to the recruitment of subjects with more severe distal radius fractures or excessive distraction during external fixation. On the other hand, the number of reduction attempts and the duration of immobilization did not predict CRPS I. Some studies have reported that careful operative techniques, the avoidance of nerve traction, and early mobilization can reduce the frequency of CRPS I after surgery [16, 34]. However, relationships between these factors and CRPS I have not been verified in clinical trials. In the clinical setting of this study, the number of reduction attempts was generally limited to two, and early mobilization was encouraged for all patients.

The pathophysiologic mechanism of CRPS I is multifactorial and relative contributions of the mechanisms underlying CRPS may differ across patients and even within a patient over times [12, 13]. Various diagnosis tools or treatment methods for CRPS I have been demonstrated, but the reliability of diagnostic tests and the

effectiveness of treatments have not been clearly proven and they have been used variably in different combination. The efficacy of imaging tools varies in terms of their sensitivity and specificity, and should be taken into account in choosing the study method. Triple-phase bone scan has better sensitivity and negative predictive values than plain radiography or magnetic resonance imaging, and it can be used to help rule out CRPS I as complimentary imaging technique [35]. For the prevention of CRPS I after a fracture of the wrist, administration of 500 mg vitamin C for 50 days has been proposed to reduce the frequency of CRPS I [21]. It has been suggested to be beneficial for other forms of trauma as a prophylactic against CRPS by acting as a hydroxyl and superoxide scavenger. Given the relationships, it becomes important to assess patient risk factors for CRPS I (female gender, severe type fracture, and high energy injury) and address issues for patients at risk with prophylactic treatment with ascorbic acid early in the recovery process. In addition, early and adequate treatment with specific anti-inflammatory drugs such as corticosteroids and radical scavengers, which have a proven therapeutic value in reducing regional inflammatory sign of CRPS [36], should be initiated for patients with CRPS I.

Study limitations include the fact that, there is no gold standard for diagnosing CRPS I, and the incidence of CRPS I after a distal radius fracture is obviously affected by the diagnostic criteria considered. In addition, the presence and severity of specific symptoms and signs are likely to show substantial variability, and physicians' or physicians' institution experience with diagnosing and treating the CRPS may influence the incidence of CRPS I. However, despite the lack of a specific test or imaging technique capable of confirming or excluding a diagnosis, the Budapest criteria for CRPS I have been widely used in previous research [21], and are increasingly used in clinical practice. Second, the pathophysiologic mechanism of CRPS I appears to be multifactorial [13], and in this study, it was not possible to consider all factors that may potentially influence its occurrence. Therefore, some potential contributors not measured in this study [12, 13] may contribute to CRPS I development. Third, this study's subjects were limited to one ethnic population drawn from an urban area, which means that their characteristics and the results may not be representative of other populations.

In conclusion, high energy injuries, severe fractures, and the female gender are risk factors for CRPS I after the surgical treatment of distal radius fracture. Given the relationships, it becomes important to assess these risk factors for CRPS I and address issues for patients at risk with prophylactic ascorbic acid and adequate treatment with anti-inflammatory drugs such as radical scavengers or corticosteroids early in the recovery process.

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