



# Understanding the Rehabilitation Needs of Korean Patients With Complex Regional Pain Syndrome

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**Objective** To evaluate the current status of pain severity and quality of life (QoL) in patients with complex regional pain syndrome (CRPS), and to assess both their perceived needs and any unmet needs of current rehabilitation services.

**Methods** A single-center questionnaire-based survey was conducted on 47 patients with CRPS who were diagnosed based on Budapest's criteria. It collected demographic and clinical data, and the structured questionnaire included the Brief Pain Inventory (BPI), the Korean version of the World Health Organization Disability Assessment Schedule II (WHODAS-K II), as well as the 5-Level EuroQol-5D (EQ-5D-5L) for measuring the QoL.

**Results** The average value of BPI and WHODAS-K II were  $7.69\% \pm 2.26\%$  and  $70.49\% \pm 19.22\%$ , respectively. In the evaluation of their perceived needs and unmet needs for rehabilitation, patients had the highest rehabilitation needs in terms of pain (95.74%), followed by bodyaches (80.85%). Regarding their unmet needs, patients had the highest unmet needs in terms of memory impairment (83.33%), followed by weight management (72.00%). According to the regression analysis, only the overall BPI was significantly associated with QoL ( $p=0.01$ ), and a higher BPI value led to poorer results for QoL.

**Conclusion** In Korea, patients with CRPS do not receive adequate rehabilitation, and they are not satisfied with current received treatments. A more structured and individualized rehabilitation treatment plan is required to manage every aspect related to chronic pain, and provision should be made for improved care guidelines for future CRPS management.

**Keywords** Complex regional pain syndromes, Quality of life, Rehabilitation

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## INTRODUCTION

Complex regional pain syndrome (CRPS) is a persistent, painful, and disabling condition that usually manifests in response to acute trauma or surgery [1]. It is a multifactorial condition with a complex cause and with a challenging diagnosis as the signs and symptoms vary over time, resulting in severe pain and disability [2]. Incidence rates from 5.46 to 26.2 per 100,000 person-years have been reported, however they were variable and dependent upon the different diagnostic criteria used in the studies [3,4]. Two types of CRPS exist: CRPS type I occurs without a nerve lesion and CRPS type II has a detectable nerve lesion. It is even more challenging to diagnose CRPS type I which is not accompanied by any peripheral neuropathy [5]. Likewise, although a debate regarding the diagnosis of CRPS still exists, diagnosis of CRPS is made based on clinical examination and by using the “Budapest” diagnostic criteria, which were approved by the International Association for the Study of Pain [6].

CRPS has a significant impact on the activity of daily living (ADL) and the quality of life (QoL) of patients due to intractable chronic pain. In particular, chronic CRPS is a challenging and complex bio-psychosocial condition which requires a comprehensive and multidisciplinary approach from direct pain management to physical and psychosocial rehabilitation [7]. Therefore, different types of interventions should be applied together and they could include appropriate medication, invasive therapies, as well as continuous rehabilitation (physical therapy and occupational therapy) [8-14].

A lot of research on the multifactorial origin and maintenance of CRPS are underway and they include studies on new or existing agents that target the different mechanisms of action. Various medications are being explored, including but not limited to steroids, non-steroid anti-inflammatory drugs, bisphosphonate, calcitonin, N-methyl-d-aspartate receptor antagonist, as well as immunomodulation therapy and botulinum toxin A [15]. Nevertheless, CRPS is still difficult to treat and it usually evolves into a chronic disease. One of the causes for this progression may be related to the lack of adequate physical and occupational treatment that should be included as a first-line of treatment for CRPS patients [16].

Rehabilitative interventions for CRPS mainly consist of several types of physical and occupational therapy

targeted at decreasing pain and edema, increasing range of motion (ROM), promoting normal sensitization, and maximizing limb or body function [12]. Rehabilitative treatments that are aimed at improving limb function and desensitization to pain are a crucial part of CRPS management. However, patients do not receive appropriate or sufficient rehabilitation treatments consistently, despite their needs. Unmet needs are defined as the gap between the needs of patients and the actual receipt of services [17]. Unmet needs for rehabilitative treatments and potential barriers to treatment access should be assessed in patients with CRPS, but their rehabilitation needs have rarely been investigated [18]. A previous qualitative study reported that a lack of access to accurate information was a major unmet need in patients with CRPS [19]. In Korea, rehabilitative treatment is not provided appropriately to patients with CRPS due to a lack of awareness of rehabilitation options available for both patients and healthcare professionals. Although physical and occupational therapy should be considered as the first-line treatment for every CRPS patient, comprehensive rehabilitation therapy is not being applied widely in clinical settings [16]. While rehabilitation for other disabilities is being well developed comparatively, institutional and policy limitations do not allow appropriate rehabilitation services for chronic pain.

Therefore, this study aimed to evaluate the current status of pain severity, pain-related disability and QoL in patients with CRPS in Korea, and to assess both their perceived needs and unmet needs for rehabilitation services.

## MATERIALS AND METHODS

### Study population

A single-center questionnaire-based survey was conducted from September 2017 to February 2019 on patients who were diagnosed with CRPS at the Seoul National University Bundang Hospital. Diagnosis according to the Budapest criteria was based on an objective physical examination in an outpatient clinic and the patient's questionnaire results to evaluate all four distinct categories: sensory, vasomotor, sudomotor/edema, and motor/trophic [3,6]. Patients were recruited from the Department of Rehabilitation Medicine through direct referral from primary care physicians and medical specialists in

other departments, such as anesthesiologic pain clinics, orthopedic surgery, or neuropsychiatry. Symptoms and signs of the patients were evaluated by a physiatrist or pain specialist according to the Budapest diagnostic criteria. In addition, data were collected only for patients who underwent a three-phase bone scan and electrodiagnosis. After diagnosis, patients who were 18 years or older and able to understand and complete the questionnaires received further information on this study. A total of 47 patients were enrolled after signing informed consents and the study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-1707-408-303).

### Assessment

Demographic characteristics, CRPS-specific questionnaires, pain, QoL and rehabilitation needs were assessed.

#### *Demographic characteristics*

Collected demographic data included the following: sex, age, marital status (living with/without spouse), religion (with/without religious beliefs), residential area (metropolitan area, city or country), educational status (high school or less/university graduation or higher), employment status (with/without a job), family history, disability judgement, and legal action.

#### *CRPS-specific questionnaires and evaluation*

The CRPS-specific questionnaire included details of the pain and symptoms associated with CRPS: age of onset, the initial event precipitating symptoms, pain location(s), duration of pain, and the worst, least, and average pain severity during the past 24 hours using numeric rating scales.

#### *Pain*

Pain intensity was assessed using the Brief Pain Inventory (BPI), a validated tool using numeric rating scales to measure both the intensity of pain and the interference with patients' life [4,20]. Severe, average, and weakest pain within 24 hours and current pain were assessed on a numeric rating scale.

#### *QoL*

General health status related QoL was assessed using the 5-Level EuroQol 5-Dimensional Questionnaire clas-

sification (EQ-5D-5L), which comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [21]. Each dimension is represented by a single item with five levels of responses: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L validation study was already conducted in Korea, but the crosswalk index value was not developed yet, so it was calculated using Japanese data [22,23].

#### *Functional evaluation*

We used the Korean version of the 36-item interviewer-administered World Health Organization Disability Assessment Schedule (WHODAS-II) [24] for the evaluation of each individual's function. Each item was linked to a 5-Likert scale: none=1, mild=2, moderate=3, severe=4, and extreme/cannot do=5. It also consists of five domains: understanding and communicating, getting around, self-care, getting along with others, and life activities. We summated the scores from every item to obtain each domain score, with a higher score indicating greater disability. Finally, each domain score and the overall WHODAS-II score were converted to a 0-100 scale.

#### *Rehabilitation needs, unmet needs and satisfaction*

Patients' needs and satisfaction levels were measured by a questionnaire related to the unmet needs of cancer survivors [25,26]. This part of the questionnaire encompassed three separate categories: (1) the rehabilitation needs of the problems related to CRPS, (2) whether the service was provided or not, and (3) satisfaction with the services if provided. Rehabilitation needs for CRPS related symptoms and discomforts were related to problems such as pain, fatigue, bodyaches, weight management, depression, memory impairment, dependent ADL, and decreased physical performance. Pain refers to pain at the site of CRPS and bodyache is general aching caused by CRPS. In the questionnaire, the unmet needs for rehabilitation services were evaluated by the following questions: "For the last year, have you had any needs regarding this problem?" To the patients who had needs for each item, an additional question "Have you received any rehabilitation services for this problem?" was asked. Those who responded "no" to this question among the patients with perceived needs were defined as the pa-

tients with unmet needs for rehabilitation services [27]. Unmet needs are expressed as the proportion of the patients with unmet needs to those with perceived needs. Lastly, satisfaction was assessed by asking the question “Have you had your needs fulfilled by the rehabilitation services?” to only those who experienced the rehabilitation service for their CRPS related problems.

**Statistical analysis**

The categorical variables are expressed in frequencies and percentages, and the continuous variables were presented as means and standard deviations.

Multiple regression analysis was performed to assess the association between QoL index (EQ-5D-5L) and demographic or clinical data in enrolled patients. To analyze the factors affecting the unmet needs of rehabilitation services, logistic regression analysis was performed with “unmet needs” as the dependent variable. Among many dependent variables (unmet needs), we selected and analyzed two of them (dependent ADL, decreased physical performance) because they correspond to the purpose and goal of rehabilitation therapy. In the case of the independent variable factors, pain (BPI overall, pain average), functional evaluation (WHODAS-II), and educational conditions were considered to be related [28,29]. Prior to the two regression analyses, correlation analysis was performed first, and then regression analysis was further analyzed by selecting only relevant variables.

A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 19.0 (IBM SPSS, Armonk, NY, USA).

**RESULTS**

**Characteristics of CRPS patients**

A total of 47 patients with CRPS were analyzed, and Table 1 shows the distribution of demographic factors, involved limbs, and self-reported symptom severity score of CPRS. The average age was 37.49±12.42 years; 27 were female (57.4%). Average weight and body mass index (BMI) were 68.24±14.02 kg and 24.95±3.97 kg/m<sup>2</sup>, respectively. The average duration from the first onset of symptoms and the questionnaire is 40.72±46.61 months. Twenty-six patients (55.3%) live alone without a spouse; 25 (53.2%) have religious beliefs; about half of the patients had graduated from high school or less education

**Table 1.** Characteristic factors of the CRPS patients

Characteristic	Value
Age of the questionnaire	37.49±12.42
Age of onset of CRPS (yr)	34.32±13.14
Duration (mo)	40.72±46.61
Weight (kg)	68.24±14.02
BMI (kg/m <sup>2</sup> )	24.95±3.97
Gender	
Male	20 (42.6)
Female	27 (57.4)
Marital status	
Living with spouse	21 (44.7)
Living without spouse	26 (55.3)
Religion	
With religious beliefs	25 (53.2)
Without religious beliefs	22 (46.8)
Residence	
Metropolitan area	23 (48.9)
City or country	24 (51.1)
Level of education	
High school or less	27 (57.4)
University or more	20 (42.6)
Employment status	
With	12 (25.5)
Without a job	35 (74.5)
Family history	1 (2.1)
Disability judgement	10 (21.2)
Legal action	9 (21.4)
Limbs involved	
Right upper limb	7 (14.9)
Left upper limbs	4 (8.5)
Right lower limb	14 (29.8)
Left lower limbs	21 (44.7)
Severity score of CRPS - self reported	
Allodynia	40 (85.1)
Temperature	45 (95.7)
Skin color	37 (78.7)
Sweating	40 (85.1)
Edema	39 (82.9)
Trophic changes	31 (66.0)
Motor changes	46 (97.9)
Decreased active ROM	45 (95.7)

Values are presented as mean±standard deviation or number (%).

CRPS, complex regional pain syndrome; BMI, body mass index; ROM, range of motion.

level (57.4%); a quarter of the patients had a job (25.5%). Family history of CRPS was reported by only 1 patient (2.1%). Ten patients (21.2%) had a disability certificate issued by the government and 9 (21.4%) have been engaged in legal battles. The majority of patients reported multiple symptoms of CRPS. The most common symptoms were motor changes (97.9%), decreased active ROM (95.7%), and temperature (95.7%) in decreasing order. Many patients noted other parts of the severity score as well; allodynia (85.1%), sweating (85.1%), edema (82.9%), and skin color (78.7%). Only 66.0% claimed trophic changes.

**Table 2.** Pain characteristics and quality of life

	Value
Pain severity	
Worst pain	8.19±1.91
Least pain	4.48±2.02
Average pain	6.24±1.70
Pain now	5.91±2.15
Improvement after therapy (24 hr, %)	31.96±21.46
Pain interference (BPI)	
Activity	7.69±2.26
Mood	7.65±2.57
Walk	6.99±3.23
Work	8.15±2.14
Relate	6.72±3.21
Sleep	8.18±2.85
Enjoy	8.26±2.19
Overall	7.66±2.12
EQ-5D-5L index	0.39±0.16
WHODAS-K II dimensions (%)	
Overall	70.49±19.22
Understanding and communicating	58.30±20.11
Getting around	70.72±22.72
Self-care	60.87±21.01
Getting along with people	62.89±26.70
Life activities	78.45±17.87
Participation in society	78.14±16.80

Values are presented as mean±standard deviation.

BPI, Brief Pain Inventory; WHODAS-K II, Korean version of the World Health Organization Disability Assessment Schedule II; EQ-5D-5L, 5-Level EuroQol 5-Dimensional Questionnaire.

## Pain and QoL

Table 2 summarizes pain intensity as BPI results. When we asked to evaluate patients' pain during the past 24 hours on the numerical rating scale, patients reported 6.24±1.70 as "average pain", 8.19±1.91 as "worst pain", and 4.48±2.02 as "least pain". The average value of patient-reported pain improvement in a 100% scale was 31.96±21.46 after treatment within 24 hours. According to BPI results, interference with enjoyment was rated the highest as 8.26±2.19, followed by work and sleep interference. Mean interference with the relationship with others was the lowest at 6.72±3.21. The average EQ-5D-5L index value is 0.39±0.16. In the WHODAS-II dimension, life activities domain was rated the highest at 78.45±17.87, followed by participation in society domains (78.14±16.80) and getting around (70.72±22.72). Understanding and communicating domains were rated the lowest as 58.30±20.11.

## Rehabilitation needs, unmet needs and satisfaction

Fig. 1 summarizes the rehabilitation needs, unmet needs, and treatment satisfaction of patients with CRPS. Patients had the highest rehabilitation needs in terms of pain (95.74%), followed by bodyaches (80.85%), and decreased physical performance (78.72%). The rehabilitation need for dependent ADL was rated the lowest as 51.06%. Regarding unmet needs, patients had the highest unmet needs in terms of memory impairment (83.33%), followed by weight management (72.00%) and fatigue (59.46%). However, the lowest of unmet needs was found in the rehabilitation need for the problems related to pain (17.78%), and the unmet needs of recovery of decreased physical performance, bodyaches, and depressive mood were also rated to be less than 40%. The highest satisfaction was found in the rehabilitation services for fatigue problems (73.93%), and the lowest was for weight management (28.57%).

## Factors associated with QoL (EQ-5D-5L) and unmet needs according to the regression analysis

Tables 3 and 4 showed the results of the multiple regression analysis examining factors that affect the EQ-5D-5L index and the logistic regression analysis examining correlated variables for unmet needs (dependent ADL and decreased physical performance), respectively. Only the overall BPI was associated with QoL ( $p=0.01$ ), where



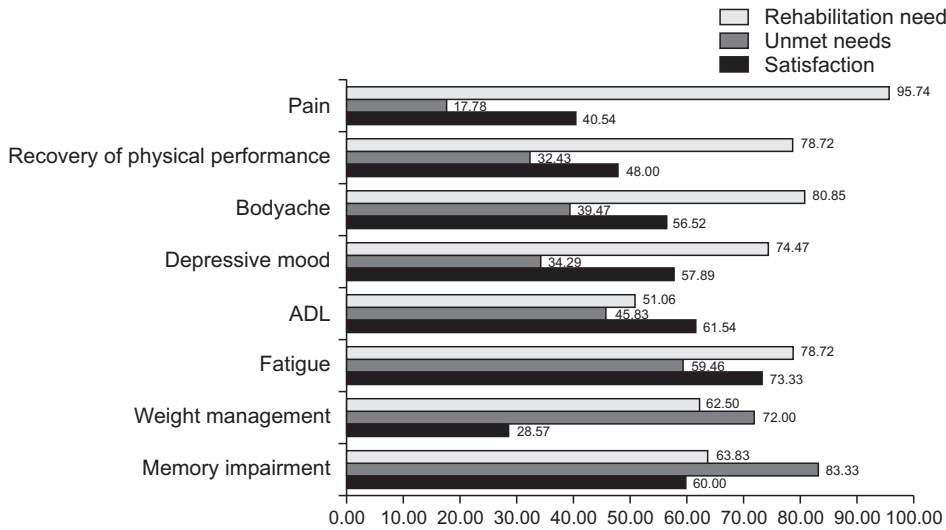


Fig. 1. Rehabilitation needs, unmet needs and satisfaction. Values are presented as percentage (%). ADL, activities of daily living.

Table 3. Multiple regression analysis for EQ-5D-5L index of CRPS patients

	B (coefficient)	95% CI	p-value
BPI_overall	-0.06	-0.08 to -0.04	0.01
WHODAS-II_overall	0		0.99
Pain_average	0		0.75

EQ-5D-5L, 5-Level EuroQol 5-Dimensional Questionnaire; CRPS, complex regional pain syndrome; BPI, Brief Pain Inventory; WHODAS, World Health Organization Disability Assessment Schedule; CI, confidence interval.

Table 4. Logistic regression analysis for unmet needs of CRPS patients

	ADL	Recovery of physical performance
WHODAS-II_overall	1.05 (0.99-1.12)	1.04 (0.98-1.10)
BPI_overall	1.07 (0.59-1.95)	0.94 (0.58-1.54)
Education	2.54 (0.56-11.50)	5.43 (1.19-24.77)*

Values are presented as odds ratio (95% confidence interval).

CRPS, complex regional pain syndrome; ADL, activities of daily living; WHODAS, World Health Organization Disability Assessment Schedule; BPI, Brief Pain Inventory.

\*p<0.05.

higher BPI values led to poorer results for QoL (low EQ-5D-5L index). Any significant factors associated with the unmet needs of ADL were not found. People with university or higher education reported more unmet needs of recovery of physical performance (odds ratio=5.43; 95% confidence interval, 1.19-24.77).

**DISCUSSION**

This study describes the current status of pain severity, QoL and its relationship with disease symptoms, and both the subjective needs and unmet needs for rehabili-

tation services of 47 patients with CRPS. CRPS symptoms were found to interfere significantly with patients' life, daily functioning, and QoL.

The QoL of CRPS patients was shown to deteriorate more when compared with other populations with activity limitations reported in previous studies [28,30]. The average EQ-5D-5L index and WHODAS-II values were 0.39 and 70.49, respectively, in this study; however, the EQ-5D-5L index measured in another study to compare treatment effects in 56 CRPS patients was 0.53 or 0.47 before treatment [31]. In one study evaluating the QoL of Korean polio survivors, the EQ-5D-5L index was 0.68

[28]. The other study of evaluating QoL in patients with traumatic brain injury (TBI) and spinal cord injury (SCI) in Thailand, WHODAS-II overall score was 66.38 for TBI patients and 52.00 for SCI patients [30]. CRPS patients in our study had the lowest level of QoL when compared to CRPS patients from other countries and other patients with severe disability. As a result, a more comprehensive and improved rehabilitation treatment approach would be necessary to further improve QoL and recovering function of patients living with CRPS. Nonetheless, although rehabilitation treatment is strongly recommended to CRPS patients, current rehabilitation specialists mainly provide only pain management therapy, instead of a coordinated multidimensional program for these patients to learn to cope with their various other symptoms and disabilities [32] (Fig. 1). Various approaches to physical and occupational therapy have been considered as key components in the management of CRPS [2,9]. Usual physical therapy has been shown to help overcome pain and pain-related symptoms such as kinesiophobia, and it improves functional use of the limb. Examples include ROM exercises, contrast baths, functional electrical stimulation, massage, and isometric strengthening exercises to overcome pain. Occupational therapy to increase the use of the affected limb in ADL, along with mirror therapy and applying garments for reducing edema or sensory overload have also been administered [8].

The unmet needs of rehabilitation treatments in CRPS patients were 48.07% overall, although there was a difference in each item. Considering that the unmet need for pain is as low as 17.78%, unmet needs for other problems are quite high (32.43%–83.33%). Currently, it is difficult to compare directly unmet needs with other studies because there have been no studies reporting the unmet needs of rehabilitation services in CRPS patients as far as we know. However, a study conducted in Denmark reported about 20% of unmet needs in cancer rehabilitation [33]. The unmet needs for medical services of SCI patients in Korea were reported as 24.8% [27]. Compared to these studies, our study reported that the unmet needs of CRPS patients in Korea are higher than those of patients with other diseases.

In Korea, even CRPS patients who did receive rehabilitation treatment were found to have low satisfaction of said treatment. Satisfaction with treatment was 53.30% overall, though variable according to each domain

(28.57%–73.33%). Regarding the rehabilitation treatment for pain, which is characterized by relatively low unmet needs, satisfaction was still low (40.54%). When investigating what treatment was given to CRPS patients, most were pain-related medications or procedures. Patients with CRPS have complex combined physical, psychological, behavioral, and emotional disabilities. CRPS rehabilitation is a process supported by therapists, family members, and carers to achieve patients' maximum potential for each domain [32]. However, CRPS treatments in Korea have focused mainly on managing pain and pain-related symptoms. Some therapists are not aware of "learned disuse" (marked disability developed as a means of avoiding pain) and its management, and they focus only on pain treatments. Our study also reported that the unmet needs in several other domains are quite high. The unmet need for pain is only 17.78%, which is the lowest, but no satisfactory improvement is seen through treatment thereof, resulting in poor satisfaction.

Characteristically, the unmet needs of weight management and memory impairment were high at 72.0% and 83.3%, respectively. In contrast, satisfaction showed opposite results; weight management 28.57%, memory impairment 60.00%. There may be several reasons for weight gain, but we surmise that limitations on activity resulted in an increase in body weight. In the domain of memory impairment, excessive use of analgesics is thought to adversely affect cognitive performance [34]. In the case of satisfaction, result interpretation is limited because a very small number of the patients actually received the treatment in respective domain (weight management=7; memory impairment=5). In this study, the absence of objective figures for weight changes and memory impairment also make result interpretation difficult. Future studies should further evaluate weight-related problems and cognitive performance of CRPS patients using specific evaluation tools.

Regression analysis was performed to clarify factors affecting unmet needs and QoL in CRPS patients. All other factors, including demographic factors, were not correlated. Only the BPI average score influenced QoL (EQ-5D-5L). Thus, pain control was found to be important as related to QoL of CRPS patients. Most rehabilitation treatments and efforts aim to control patients' pain, but satisfaction is low as confirmed in this study (40.54%). The reasons for low satisfaction should be further in-

investigated, and we should attempt to find and apply effective treatment methods. For example, graded motor imaginary therapy has been highlighted as a mechanism-based approach for the treatment of CRPS [35]. In a recent systematic review, graded motor imaginary therapy and mirror therapy may provide clinically meaningful improvements in patients with CRPS, although the quality of the supporting evidence is very low [9]. The logistic regression analysis to find the causes of the unmet needs suggests that only “education level” affects the unmet need of “decreased physical performance”. Reasons for unmet needs for rehabilitation are multi-dimensional and complex. Many studies indicate that barriers to accessing medical services, educational levels, and household income were essential determinants of unmet needs [27,28,36]. Our research also supports that lower educational attainment increases the unmet need of a health care system. Educational level affects those with lower socio-economic status more, and this implies that individuals with lower educational levels have more barriers to overcome to access medical systems [29,37].

### Limitation

The findings of this study need to be carefully interpreted because of the small number of participants. Since CRPS is a rare disease and patients were recruited from a single tertiary care facility, we could not recruit enough patients. In our study, we evaluated the current status of QoL of CRPS patients and the unmet needs of current rehabilitation services. Therefore, there was a lack of evaluation and research on the causes of unmet needs. Accessibility of medical services has been considered to be the main cause of unmet need, and the questionnaire was divided into several questions to identify the cause of unmet need [36,38]. Further study on the causes of unmet needs is needed, combining the results of logistic regression and the results of other studies.

In addition, our study was conducted as a cross-sectional survey, and not a longitudinal cohort study. However, other cohort studies such as in the Netherlands, Switzerland, the United States, and the UK concentrated mostly on demographic and clinical phenotypic factors. There has also been a lack of evidence about currently given rehabilitation treatment and the perceived unmet needs of CRPS patients visiting a specialist in the department of rehabilitation [3,4,39,40]. On the other hand, we

were actively recruiting well-defined CRPS patients and especially pointed out the available rehabilitation treatments at present, with concurrent unmet and satisfying needs, as well as QoL of enrolled patients.

### Conclusion

Current management of CRPS focuses on managing pain and pain-related symptoms using both medical management and rehabilitation therapy. Patients with CRPS do not receive adequate rehabilitation, and they are not satisfied with current received treatments. The unmet needs reported from our study would help to identify a better therapeutic strategy and hopefully would improve treatment outcome in patients with CRPS in the future. The diverse biochemical and clinical characteristics according to the severity and chronicity of the disease should be considered, and a tailored therapeutic strategy to overcome not only the pain and pain-related symptoms but also other unmet needs such as the recovery of physical performance, depressive mood, fatigue, weight management, and memory impairment should be prepared, according to the heterogeneity of the CRPS population.

### CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

### AUTHOR CONTRIBUTION

Conceptualization: Lim JY, Kim IS, Hyun SE, Park JH. Methodology: Lim JY, Kim IS, Hyun SE. Formal analysis: Lim JY, Kim IS. Project administration: Lim JY, Kim IS. Visualization: Lim JY, Kim IS, Hyun SE, Park JH. Writing – original draft: Lim JY, Kim IS, Hyun SE, Park JH. Writing – review and editing: Lim JY, Kim IS. Approval of final manuscript: all authors.

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