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NEUROPATHIC PAIN SECTION

Is there an association between serum soluble interleukin-2 receptor levels and syndrome severity in persistent Complex Regional Pain Syndrome?

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Abstract

Objective: A potentially useful biomarker for Complex Regional Pain Syndrome (CRPS) is the serum soluble interleukin-2 receptor (sIL-2R) level, which is a marker for T-cell activation. Elevated serum sIL-2R levels have been described in CRPS patients compared to healthy controls. In T-cell mediated inflammatory diseases such as sarcoidosis and rheumatoid arthritis, the serum sIL-2R levels correlate with disease severity. In this study, we investigate whether an association exists between serum sIL-2R levels in CRPS patients and CRPS severity.

Methods: A cross-sectional cohort study was conducted in a tertiary pain referral center in the Netherlands. Adult CRPS patients diagnosed by the IASP criteria were included between October 2018 until October 2022. The main study parameters were serum sIL-2R levels and the CRPS severity score.

Results: Fifty-three CRPS patients were included with a mean syndrome duration of 84 months (Q3 – Q1:180 – 48). The majority had persistent CRPS with a syndrome duration >1 year ($n = 52$, 98%). The median pain Numerical Rating Score (NRS) was 7 (Q3 – Q1: 8 – 5) and the mean CRPS severity score was 11 (SD ± 2.3). The median serum sIL-2R level was 330 U/mL (Q3 – Q1:451 – 256). No statistically significant correlation was observed between serum sIL-2R levels and the CRPS severity score ($r_s = 0.15$, $P = .28$).

Conclusions: Our findings suggest that serum sIL-2R levels cannot be used as a biomarker for syndrome severity in persistent CRPS (syndrome duration >1 year). Serial measurements of serum sIL-2R from early CRPS to persistent CRPS are needed to investigate whether serum sIL-2R levels can be used to monitor T-cell mediated inflammatory syndrome activity.

Keywords: CRPS; sIL-2R; soluble interleukin-2 receptor; inflammation; biomarker; severity

Introduction

Complex Regional Pain Syndrome (CRPS) is characterized by continuous pain and various sensory, motor, vasomotor, sudomotor, and trophic disturbances.[1] These signs and symptoms are incorporated in the clinical diagnostic criteria for CRPS by the International Association for the Study of Pain (IASP).[1] The onset of CRPS is preceded by tissue damage to an extremity, due to, for example, a fracture or surgery.[2,3] After tissue damage, multiple underlying mechanisms such as inflammation, central sensitization, vasomotor disturbances, and motor disturbances play a role in the onset and/or maintenance of CRPS.[4] For the management of each CRPS patient, the most prominent mechanism(s) must be assessed and targeted in a mechanism-based manner. A considerable proportion of patients with early CRPS improve or recover with standard care.[5] However, a smaller proportion of the CRPS population does not significantly improve and may go on to develop prolonged and intractable CRPS, which is called persistent CRPS nowadays.[5] This transition from early to persistent CRPS was discussed in an expert meeting in Valencia and seems to occur during the first 12–18 months after onset, although there is no broad consensus on the demarcation point for this distinction.[5]

There is still no clear biochemical measure for monitoring syndrome severity. The only useful test seems to be the CRPS Severity Score, which is a sum-score based on clinical signs and symptoms of this syndrome.[6] The CRPS severity score discriminates well between CRPS and non-CRPS patients and a higher CRPS severity score is associated with significantly higher clinical pain intensity, distress, and functional impairments as well as greater bilateral temperature asymmetry and thermal perception abnormalities.[6,7] A limitation of the CRPS severity score is that physicians must rely on subjective symptoms reported by patients and relatively subjective signs observed during physical examination. In addition, discrepancy between the symptoms and signs, and the heterogeneous presentation of CRPS complicate the monitoring of CRPS severity.

Because of these limitations, a biomarker of syndrome severity or activity would be of great value in the management of CRPS. Unfortunately, no objective and easily measurable biomarkers have yet been identified in CRPS to support

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diagnosis and management.[8,9] A potentially useful biomarker for CRPS is the serum soluble interleukin-2 receptor (sIL-2R) level, which is a marker for T-cell activation.[8,10] Our research group measured serum sIL-2R levels in CRPS patients and healthy controls and found significantly higher serum sIL-2R levels in the CRPS patients than in controls.[11] This finding indicated increased T-cell activity in CRPS and led us to hypothesize an altered T-cell regulation and possible T-cell mediated inflammation in CRPS.[11–13] In T-cell mediated diseases such as sarcoidosis and rheumatoid arthritis, serum sIL-2R levels correlate with disease severity.[14–16] However, it is unknown if there is an association between the serum levels of sIL-2R and the severity of CRPS.

The aim of this study was to investigate whether a potential association exists between serum sIL-2R levels and syndrome severity in patients with CRPS.

Methods

Ethical approval

Ethical approval for this cohort study was obtained from the Medical Ethics Committee of Erasmus MC University Medical Center Rotterdam (MEC-2018–132). This study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Before the start of the study, written informed consent was obtained from all included patients with CRPS.

Study design and study setting

This cross-sectional cohort study was conducted at the outpatient clinic of the Center for Pain Medicine at Erasmus MC University Medical Center in Rotterdam. The Center for Pain Medicine is a tertiary referral center with clinical expertise in CRPS.

Patients

Adult patients with only 1 extremity affected by CRPS were eligible for inclusion. CRPS was diagnosed according to the IASP clinical diagnostic criteria for CRPS.[1] Consecutive patients were included between October 2018 until October 2022 during visits at the outpatient clinic of the Center for Pain Medicine. Patients were excluded if they had one or more of the following criteria: a history of an auto-inflammatory or autoimmune disease; current treatment with immunomodulating medication or treatment within the last 6 months; illness in the past 2 weeks or at the time of the visit; and suspected or confirmed pregnancy.

Study variables, measurements, and data collection

The main study parameters were serum sIL-2R levels and the CRPS severity score.[1] The sIL-2R levels and the CRPS severity score were assessed during the same outpatient visit. The CRPS severity score- Database Form developed by Harden et al.[7] was used to assess symptoms and signs of CRPS. Based on this form, symptoms of continuing, disproportionate pain, allodynia or hyperalgesia, temperature asymmetry, color asymmetry, sweating asymmetry, edema, dystrophic changes and motor abnormalities were asked during history taking. Other parameters that were asked during history taking were: age, gender, duration of CRPS in months (ie, duration of symptoms and signs), precipitating injury (ie, initiating factor of symptoms and signs), affected extremity by CRPS, pain medication, intensity of pain at the moment of the outpatient visit and in the past 24 hours measured by an 11-point Numeric Rating Scale (NRS).

During physical examination, signs of hyperalgesia to single pinprick, allodynia, temperature asymmetry by palpation, color asymmetry, sweating asymmetry, asymmetric edema, dystrophic changes, and motor abnormalities were assessed using the instructions of the CRPS severity score- Database Form.[7] For each patient, all symptoms and signs were scored and summated for the total CRPS Severity Score, with scores that could range from 0 to 16.[7]

Assessment of serum sIL-2R levels

During the outpatient visit, a 5-mL tube of venous blood was drawn to determine the serum sIL-2R level. After collection, the venous blood samples were centrifuged at 3000 rpm, and serum was subsequently isolated. Serum sIL-2R levels were determined at the laboratory of medical immunology at Erasmus MC under strict ISO15189 regulations. For this study, October 2018 to October 2019 serum sIL-2R levels were determined with ELISA (Human sCD25/sIL2R, Diaclone, Besancon, Cedex, France) and reported in picograms per milliliter (pg/mL) as previously used in studies by our group.[11,17] During this study the laboratory of medical immunology replaced the routinely used ELISA for sIL-2R detection by an automated immune assay based on chemiluminescence (IMMULITE 2000 IL2R assay: Siemens Healthcare, Germany) that reports serum sIL-2R levels in units/milliliter (U/mL) and for which serum sIL-2R levels $\geq$555 U/mL are considered elevated. For our current study, samples included from October 2019 were measured with this new assay. Internal validation of the laboratory of medical immunology at Erasmus MC revealed that although both systems report different values in different units (pg/mL vs U/mL) there is perfect correlation between both methods. Furthermore, a parallel analysis of 50 serum samples forms healthy blood donors and 28 routine diagnostic samples with the ELISA and the IMMULITE IL2R assay revealed that the serum sIL-2R generated in pg/mL by ELISA can be converted to U/mL by dividing the value by 6.4.[10]

Study size

As no results of previous studies were available at the time of designing and initiation of the study in 2018, a statistically detectable and clinically relevant effect size (f2) of 0.25 was chosen for four parameters: serum sIL-2R level, gender, age and duration of the syndrome. The power of the study (1 - β) was chosen to be 0.8 and the 2-sided level of significance (α, 2 tailed) to be 0.05. The required a priori total sample size computed by this method was 53 CRPS patients.

Statistical analysis

Descriptive statistics were used to describe the frequencies of the demographic variables and the serum sIL-2R level and to describe measures of central tendency and variability, dependent on the shape of their distribution. The Shapiro-Wilk test was used to analyze whether the primary outcome parameters were normally distributed. A potential association between serum sIL-2R levels and age, the CRPS severity score and the duration of CRPS was explored using either a Pearson's correlation or a Spearman's rank correlation, dependent on the shape of the distribution of these variables. Continuous

variables were compared between 2 groups with the 2-sided independent *t*-test or a 2-sided Mann-Whitney *U* test, dependent on the shape of distribution. Comparison of continuous variables between more than 2 groups was conducted using either an ANOVA or a Kruskal-Wallis test, dependent on the shape of distribution. Correction for multiple testing was performed using the Bonferroni method by multiplying each reported *P* values by the number of comparisons that were conducted. The alpha level for statistical significance was set at 0.05. Analyses were performed using IBM SPSS Statistics 21.

Results

Patients

A total of 66 patients were approached to participate in this study (Figure 1). Twelve patients were excluded from the study. Five patients declined to participate. One patient had multiple extremities that were affected by CRPS. One patient used prednisone. Five patients were excluded because the patients did not meet the IASP criteria for CRPS anymore. One patient did not show up to the outpatient clinic appointment. A total of 53 patients were included for analysis.

The majority of included patients were female (92.5%) and had a mean age of 44 (SD ± 14.9) years. The median pain score was 7 (Q3 – Q1: 8 – 6). The median serum sIL-2R was 330 U/mL (Q3 – Q1: 451 – 255 U/mL). All the patients' characteristics are depicted in Table 1.

CRPS characteristics

The median CRPS syndrome duration was 84 months (Q3 – Q1: 180 – 48 months). In total, 52 out of 53 had persistent CRPS with a syndrome duration of more than 1 year (98%). Only 1 patient had early CRPS with a duration of 5 months. The CRPS duration in years of the included CRPS patients is depicted in a histogram (Figure 2). The mean CRPS severity score was 11 (SD ± 2.3). Fifty-two of the 53 patients (98%) had symptoms of allodynia and/or hyperalgesia. Hyperalgesia to pinprick was observed in 42 out of 53 patients (79%), and allodynia was observed in 48 out of 53 patients (91%). Temperature asymmetry symptoms were reported by 51 out of 53 patients (96%). Twenty-four (45%) patients had signs of a cooler affected side, and 5 (9%) patients had a warmer affected side. All 53 patients had symptoms of motor abnormalities. Signs of weakness were observed in 44 patients (83%), and a decreased active range of motion was observed in 37 patients (70%). A complete overview of the symptoms and signs of the included CRPS patients is shown in Table 2.

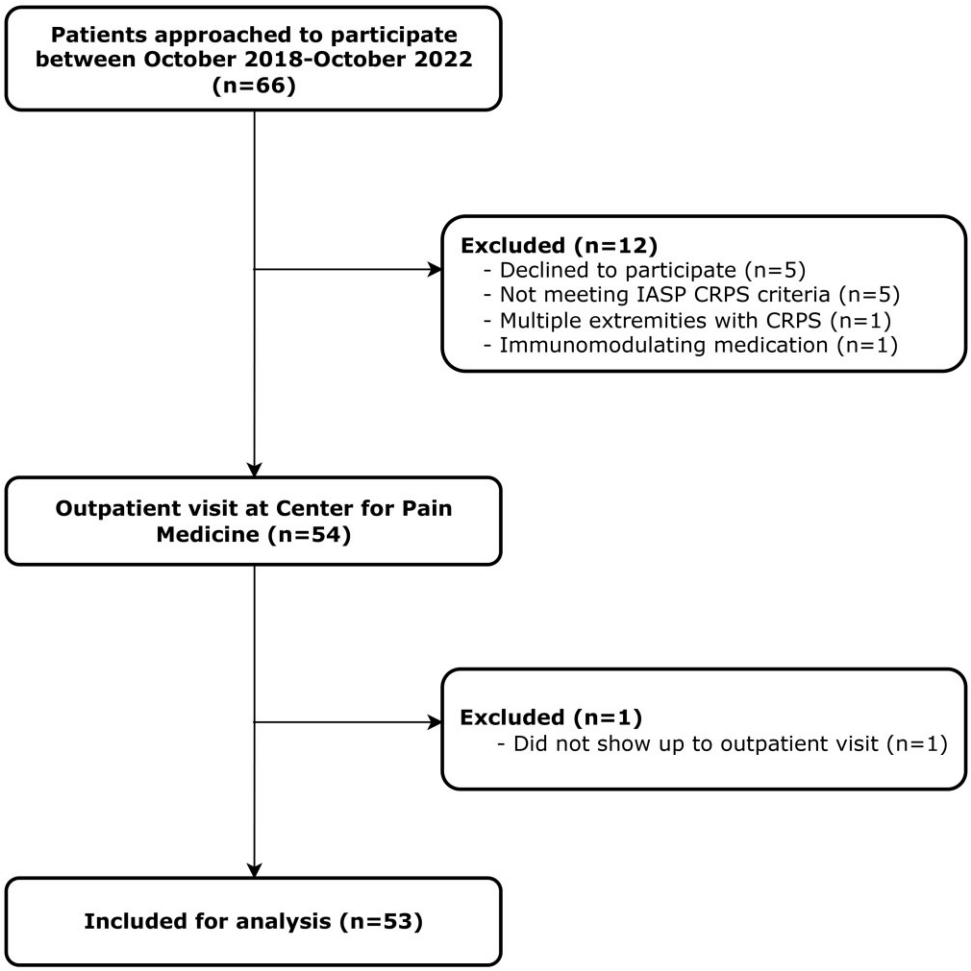

Figure 1. Flowchart of the inclusion of patients with CRPS.

Abbreviations: CRPS = Complex Regional Pain Syndrome; IASP = the International Association for the Study of Pain.

Table 1. CRPS patients' demographics and general characteristics.

	$n = 53$
Age in years (mean, SD)	44 (SD ± 14.9)
Gender (*n*, %)	
Male	4 (7.5%)
Female	49 (92.5%)
Duration of CRPS disease in months (median, Q3 – Q1)	84 (180 – 48)
Precipitating injury (*n*, %)	
Trauma	34 (64%)
Operation	14 (26%)
Spontaneous	2 (4%)
Other	1 (2%)
Unknown	2 (4%)
Affected extremity (*n*, %)	
Upper extremity right	9 (17%)
Upper extremity left	7 (13%)
Lower extremity right	17 (32%)
Lower extremity left	20 (38%)
NRS pain score at time of visit (median, Q3 – Q1)	7 (8 – 5)
NRS pain score last 24 h (median, Q3 – Q1)	7 (8 – 6)
Medication at time of visit (*n*, %)	
Paracetamol	25 (47%)
NSAIDs	9 (17%)
Opioids	22 (42%)
Antidepressants	14 (26%)
Anti-epileptics	15 (28%)
Calcium channel blocker	3 (6%)
Phosphodiesterase inhibitor	0 (0%)
Vitamin C	10 (19%)
Fluimucil or N-acetylcysteine	1 (2%)
DMSO	2 (4%)
CRPS severity score (mean, SD)	11 (SD ± 2.3)
sIL-2R level in U/mL (median, Q3 – Q1)	330 (451 – 255)

Abbreviations: DMSO = dimethylsulfoxide cream; IQR = interquartile range; NSAIDs = non-steroidal anti-inflammatory drugs; NRS = Numeric Rating Scale; SD = standard deviation.

No correlation between serum sIL-2R levels and CRPS severity

No statistically significant correlation was observed between serum sIL-2R levels and CRPS duration (Figure 3; $r_s = 0.12$, $P = .39$). In addition, no statistically significant correlation was observed between serum sIL-2R levels and the CRPS severity score (Figure 4; $r_s = 0.15$, $P = .28$). Furthermore, there was no statistically significant correlation between serum sIL-2R levels and age ($r_s = 0.04$. $P = .81$).

Discussion

Biomarkers hold the potential to monitor syndrome severity in patients with CRPS and may thereby assist in the diagnosis and management of these patients. The T-cell activation marker sIL-2R is a biomarker with potential application in the management of CRPS by means of, for example, monitoring syndrome severity. Our research group hypothesized that there is an association between the level of serum sIL-2R and CRPS severity. In this cross-sectional study, the majority of patients (98%) had persistent CRPS. In this group of patients, no statistically significant correlation was found between the level of serum sIL-2R and the syndrome severity of CRPS. Therefore, serum sIL-2R levels cannot be used as a biomarker for syndrome severity in persistent CRPS. However, in line with diseases such as sarcoidosis,[16] rheumatoid arthritis,[18] and IgG4-related disease,[19] serum sIL-2R might be useful as a biomarker for T-cell mediated inflammatory disease activity.

Our research group found no significant correlation between the serum sIL-2R levels and the severity of CRPS. This might be explained by the fact that the majority of the included CRPS patients had persistent CRPS (98%). Therefore, conclusions on the association of serum sIL-2R levels and syndrome severity can only be made for persistent CRPS. However, our research group cannot rule out that

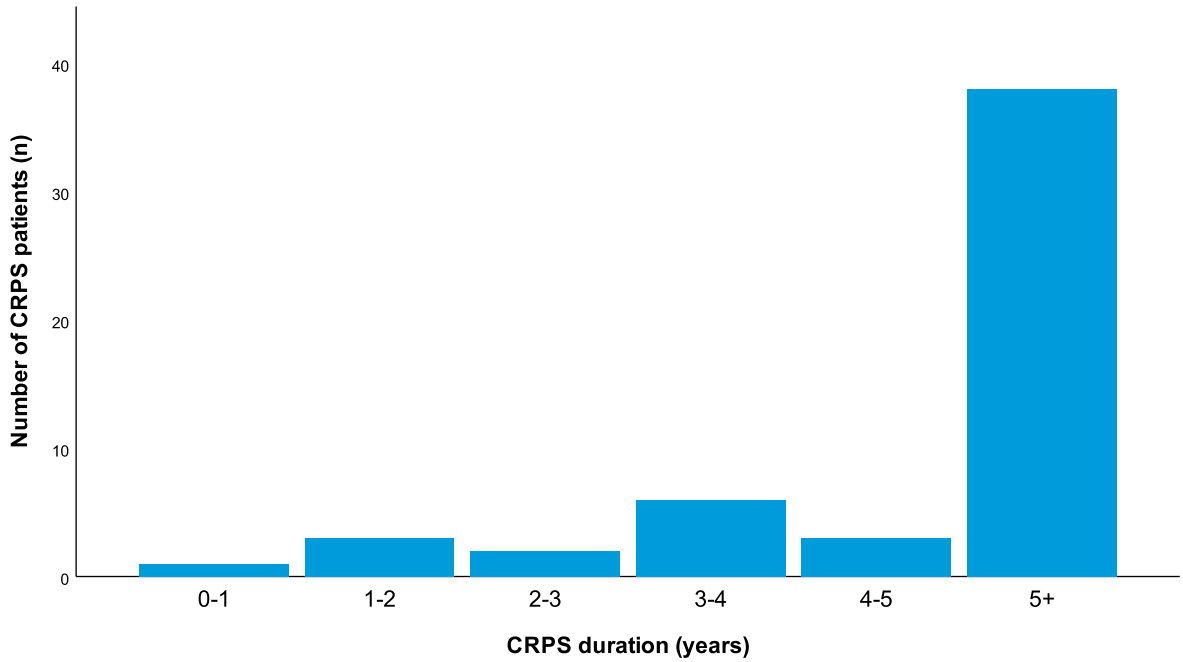

Figure 2. Histogram of the CRPS duration of the included CRPS patients in this study.
Abbreviation: CRPS = Complex Regional Pain Syndrome.

Table 2. CRPS severity score-Database Form: presence of symptoms and signs of CRPS[7].

	$N = 53$
Symptoms	
NRS at time of visit (median, Q3 – Q1)	7 (8 – 5)
NRS 24 hours before visit (median, IQR)	7 (8 – 6)
Continuing pain (n, %)	51 (96%)
Allodynia and/or hyperalgesia	52 (98%)
Allodynia	44 (83%)
Hyperalgesia	47 (89%)
Temperature asymmetry	51 (96%)
Affected side warmer	9 (17%)
Affected side colder	30 (57%)
Affected side warm/cold	13 (25%)
Color asymmetry	41 (77%)
Red	23 (43%)
Blue	24 (45%)
Other color	17 (32%)
Sweating asymmetry	25 (47%)
Edema	46 (87%)
Dystrophic changes	37 (70%)
Nails	31 (58%)
Hair	24 (45%)
Skin	15 (28%)
Motor abnormalities	53 (100%)
Weakness	53 (100%)
Tremor	26 (49%)
Dystonia	25 (47%)
Decreased AROM	42 (79%)
Myoclonus	16 (30%)
Signs	
Hyperalgesia to pinprick	42 (79%)
Allodynia	48 (91%)
Light touch	37 (70%)
Deep joint pressure	42 (79%)
Vibration	35 (66%)
Cold	21 (40%)
Heat	21 (40%)
Temp asymmetry on palpation	29 (55%)
Affected side cooler	24 (45%)
Affected side warmer	5 (9%)
Color asymmetry	21 (40%)
Red	15 (28%)
Blue or Pale	8 (15%)
Mottled	4 (8%)
Scar	0 (0%)
Sweating asymmetry	4 (8%)
Increased on affected side	4 (8%)
Decreased on affected side	0 (0%)
Asymmetric edema	24 (45%)
Dystrophic changes	12 (23%)
Nails	8 (15%)
Hair	3 (6%)
Skin	5 (9%)
Motor abnormalities affected side	50 (94%)
Tremor or myoclonus	4 (8%)
Dystonia	9 (17%)
Decreased AROM	37 (70%)
Weakness 1/5[a]	10 (19%)
Weakness 2/5[b]	4 (8%)
Weakness 3/5[c]	5 (9%)
Weakness 4/5[d]	25 (47%)
CRPS severity score (mean, SD)	11 (SD ± 2.3)

[a] Weakness 1/5: flicker of movement.
[b] Weakness 2/5: movement with gravity.
[c] Weakness 3/5: movement against gravity.
[d] Weakness 4/5: weak.

serum sIL-2R levels do correlate with CRPS severity in early CRPS. In persistent CRPS, inflammation is often diminished,[9,20,21] and this may explain the relatively low serum sIL-2R levels measured in this study. After inflammation diminishes, influences of central sensitization, vasomotor and motor disturbances gain the upper hand[4] and result in the reported relatively high syndrome severity. Regarding the syndrome severity, the narrow distribution of the relatively high CRPS severity score (11 SD ± 2.3) is comparable to other studies with persistent CRPS patients (11.2 SD ± 2.3[7] and 11.4 SD ± 2.2[17]). In addition, Harden et al. showed that the degree of stability in the CRPS severity score was nearly twice as large in the persistent CRPS group than in the early CRPS group.[7] The relatively narrow distribution of the CRPS severity score could also explain why no statistically significant correlation was found between the serum sIL-2R levels and the severity of CRPS.

In a recently published study by our research group—that was primarily conducted to investigate whether serum sIL-2R could differentiate CRPS form other pain conditions of an extremity—we reported a negative correlation between serum sIL-2R levels and the CRPS severity score in a small group of CRPS patients.[17] Interestingly, our current study did not confirm this correlation. We cannot exclude that this is related to the larger sample size of our current study. However, in our current study the syndrome duration was significantly longer than in our previous studies. In addition, as discussed above, the serum sIL-2R levels might be reduced in persistent CRPS and the stability of the CRPS severity score increases in persistent CRPS compared to early CRPS.[7]

Although our sample size was too limited to statistically identify relevant clinical subgroups in this cohort, we can describe the most prominent CRPS characteristics. The majority of patients in this cohort had persistent CRPS and most patients had signs of hyperalgesia, allodynia, weakness and a decreased active range of motion. These signs are probably not directly caused by increased T-cell activity but are more likely to be the result of central reorganization that may correspond with the possible "central" CRPS subgroup found in a cluster analysis by Dimova et al.[22] This subgroup was characterized by signs likely originating from central maladaptive plasticity including motor deficits, minor injury, allodynia and sensory deficits.[22] This subgroup was differentiated from its counterpart-the "peripheral" subgroup-with more inflammatory signs like changes in skin color, temperature, sweating and edema.[22] Another cluster analysis by Bruehl et al. identified a warm and cold CRPS subgroup.[20] Warm CRPS patients were characterized by a warm, red, edematous and sweaty extremity and cold CRPS patients were characterized by a cold, blue, and less edematous extremity.[20] If temperature asymmetry was observed in this study, the CRPS patients were mostly cold (45% cold vs 9% warm). We expect that these cold persistent CRPS patients in our study could be comparable to the cold CRPS subgroup reported by Bruehl et al.[20] In this cluster analysis, the authors report that the inflammatory mechanisms in cold CRPS patients usually diminish by the first year post injury.[20] Therefore, our included persistent CRPS patients with cold signs may not

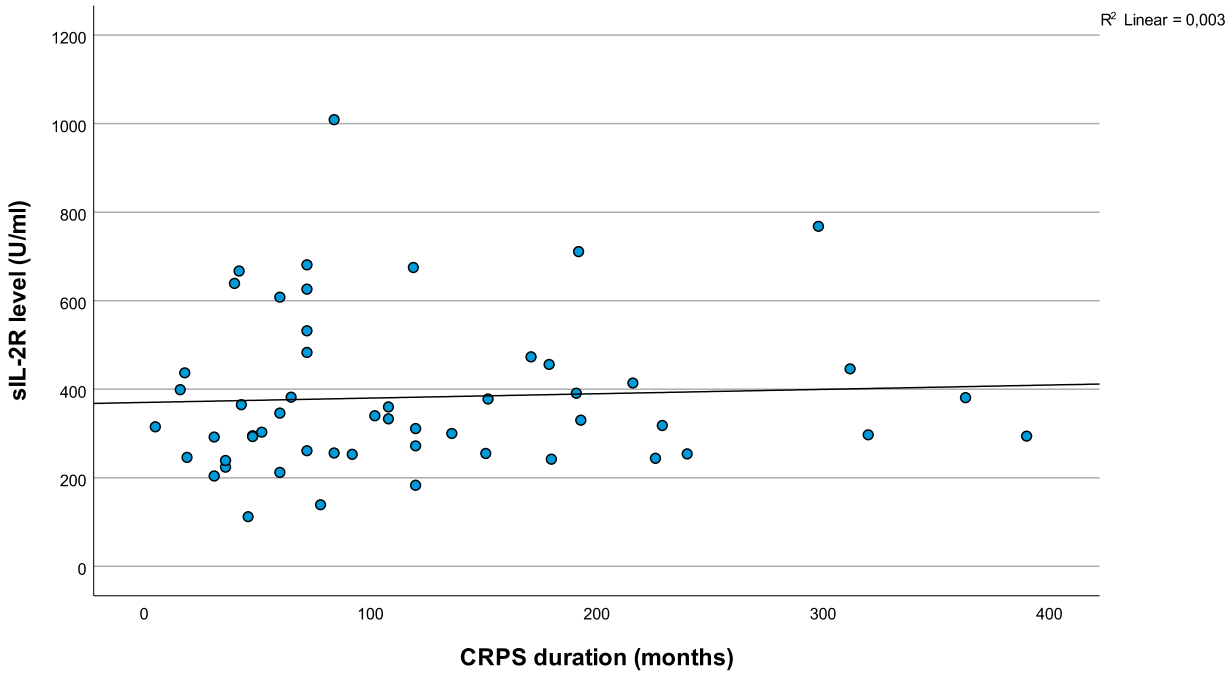

Figure 3. Scatter plot showing no correlation between serum sIL-2R level and CRPS duration in persistent CRPS patients: $r_s = 0.12$, $P = .39$.
Abbreviations: CRPS = Complex Regional Pain Syndrome; sIL-2R = soluble Interleukin-2 receptor.

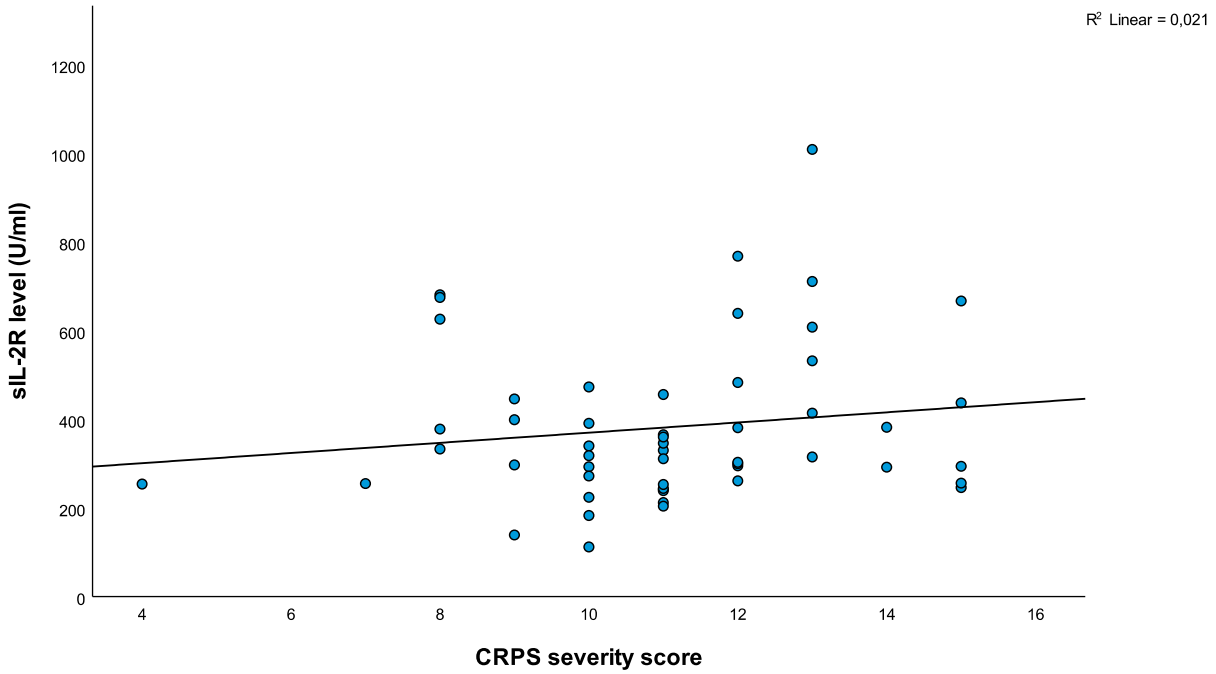

Figure 4. Scatter plot showing no correlation between serum sIL-2R level and CRPS severity score in persistent CRPS patients: $r_s = 0.15$, $P = .28$.
Abbreviations: CRPS = Complex Regional Pain Syndrome; sIL-2R = soluble Interleukin-2 receptor.
CRPS severity score: In the CRPS severity score, several clinical signs and symptoms are scored and the sum of the score reflects the severity of CRPS.[6]

have an inflammatory profile, which is further supported by the relatively low serum sIL-2R levels.

This study has several limitations. First, all but one of the included patients in this study had persistent CRPS with a long syndrome duration. This can be explained by the fact that in our tertiary referral center, we mostly treat the most complex patients that are refractory to therapy. Consequently, the included CRPS patient population does not represent the general CRPS patient population. However, especially for patients with CRPS that is refractory to treatment, it is crucial to investigate biomarkers as these can have major implications for the treatment strategy. Second, the IASP clinical diagnostic criteria for CRPS are very broad and are not aimed at selecting a specific CRPS phenotype.[4] Third, the different measurement techniques for analyzing serum sIL-2R levels during the study could be a potential limitation.

However, the manual ELISA system and the automated Immulite IL2R assay showed a perfect correlation between each other.[10] Fourth, although patients with immunomodulating medication within the last 6 months were excluded, there were no adjustments made for other therapies that may interfere with inflammation and/or syndrome severity such as physiotherapy[23] or spinal cord stimulation.[24] However, these therapies are essential for the management of persistent CRPS and the influence of these therapies on serum sIL-2R levels is still unclear. Fifth, both the innate and adaptive arm of the immune system can be affected in CRPS patients[25] and therefore, besides serum sIL-2R, various other potential biomarkers have been identified that may be useful in monitoring inflammation in CRPS.[8,9] Other immune molecules such as cytokines or other soluble surface molecules produced by activated immune cells may also be potential interesting biomarkers.[8] Of note, during the course of the syndrome, the pathophysiological mechanisms contributing to CRPS signs and symptoms may change.[4] We consider it therefore unlikely that a single biomarker will cover all these different pathophysiological mechanisms over the course of the syndrome, and it is possible that different biomarkers are needed for the early and persistent phase of CRPS.[8,9]

Expert opinion: relation between serum sIL-2R levels, CRPS severity and syndrome duration

In a post hoc analysis, our group compared the serum sIL-2R levels obtained from 75 healthy donors (306 U/mL; Q3 – Q1: 404 – 256) and the serum sIL-2R levels obtained in the current study (330 U/mL; Q3 – Q1: 451 – 256). There was no statistically significant difference between the serum sIL-2R level of persistent CRPS patients and healthy controls ($P = .229$) (Figure 5). We consecutively compared serum sIL-2R levels with previous studies conducted by our research group. The current study reported the lowest median serum sIL-2R level of 330 U/ml with the longest median syndrome duration of 84 months. A previous study reported a higher median serum sIL-2R level of 439 U/mL that was obtained from patients with a shorter median CRPS duration of 26 months.[17] In addition, an even higher median serum sIL-2R level of 649 U/mL was obtained from patients with the shortest median CRPS duration of 11 months.[11] When comparing these datasets, we can conclude that a longer syndrome duration is associated with lower or even normalized serum sIL-2R levels (Figure 5). Decreased T-cell activity with CRPS progression is further supported by the statistically significant negative correlation between serum sIL-2R levels and the CRPS duration when the data of the current study and the studies by Bharwani et al.[11,17] are combined (Figure 6).

The findings of the post-hoc analysis suggest that serum sIL-2R levels are related to the duration of CRPS. Based on the transition from early to persistent CRPS, we present a hypothetical model of the relationship between inflammation involving T-cell activity and CRPS severity during the progression of CRPS (Figure 7).[26] In our model, T-cell activity in CRPS changes during different phases of the syndrome (ie, early and persistent CRPS). During the first months after onset of CRPS signs and symptoms, it is recognized that post-traumatic inflammatory immune activation is most prominent.[4,9,20,21,25] In early CRPS, most patients have classic signs of inflammation such a red, swollen, warm and dysfunctional

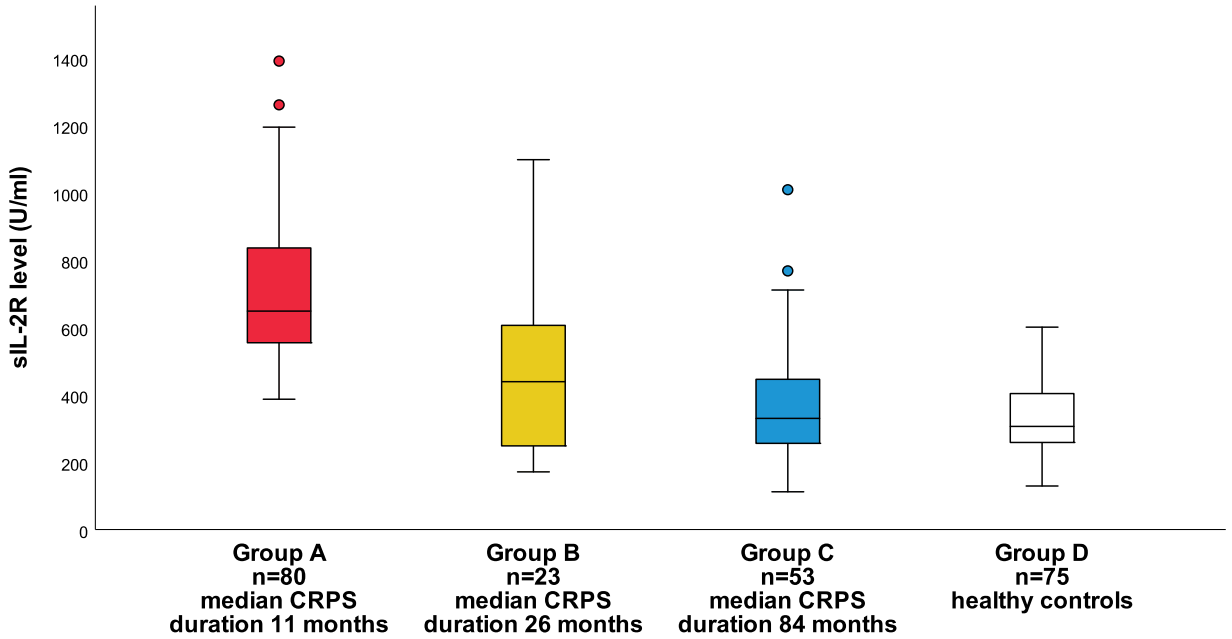

Figure 5. Boxplot of median serum sIL-2R levels in recent studies with patients with CRPS and a group of healthy controls. Group A is the trial by Bharwani et al. from 2017[11] with a median serum sIL-2R of 649 U/mL (Q3 – Q1: 895 – 554) and a median CRPS duration of 11 months (Q3 – Q1: 36 – 5). Group B is the trial by Bharwani et al. from 2020[17] with a median serum sIL-2R of 439 U/mL (Q3 – Q1; 611 – 248) and a median CRPS duration of 26 months (Q3 – Q1: 81 – 14). Group C is the current trial with a median serum sIL-2R of 330 U/mL (Q3 – Q1; 451 – 256) and a median CRPS duration of 84 months (Q3 – Q1: 180 – 48). Group D is a group of healthy controls with a median sIL-2R level of 306 U/mL (Q3 – Q1: 404 – 256).Group A vs Group B vs Group C vs Group D: $P < .001$. Group A vs Group C, $P < .001$*. Group B vs Group C, $P = .795$*. Group D vs Group C, $P = .687$*. *P value after Bonferroni correction.

Boxplot legend: median (midline), box (25th to 75th percentiles), and whiskers. Outliers are shown with circles.

Abbreviations: CRPS = Complex Regional Pain Syndrome; sIL-2R = soluble interleukin-2 receptor.

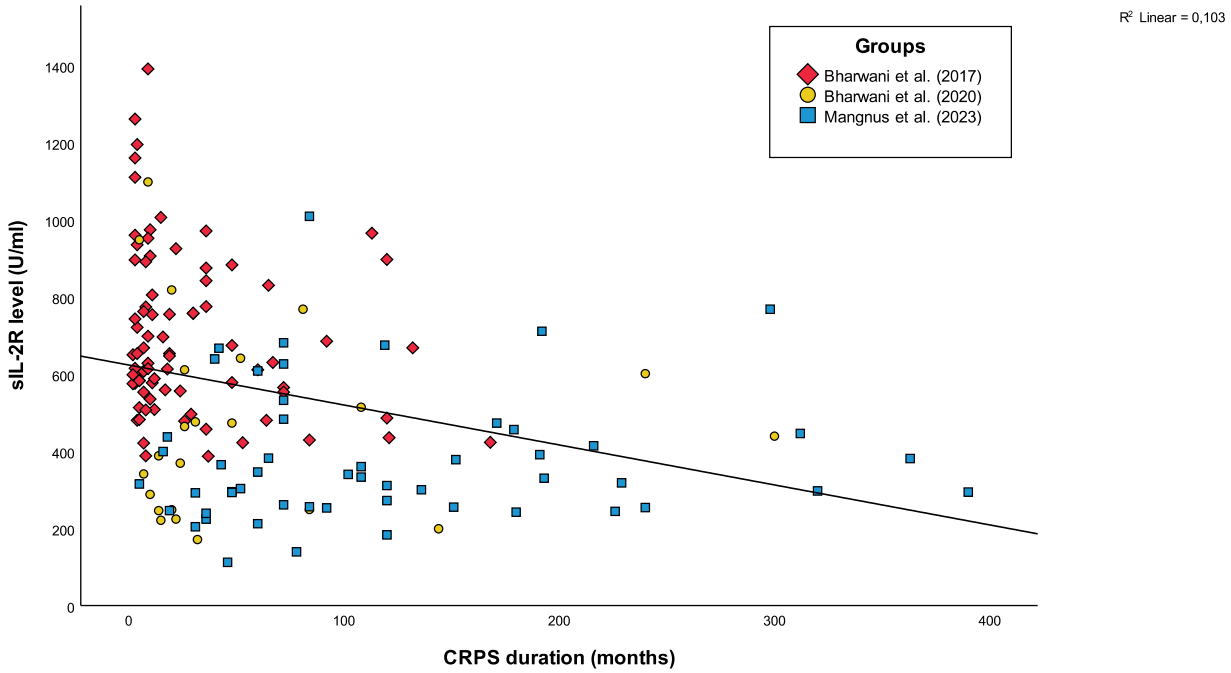

Figure 6. Scatter plot showing the correlation between serum sIL-2R level and CRPS duration in the CRPS patients included in this current trial and the trials by Bharwani et al.[11,17] ($n = 156$: $r_s = -0.407$, $P = < .001$).

Abbreviations: CRPS = Complex Regional Pain Syndrome; sIL-2R = soluble Interleukin-2 receptor.

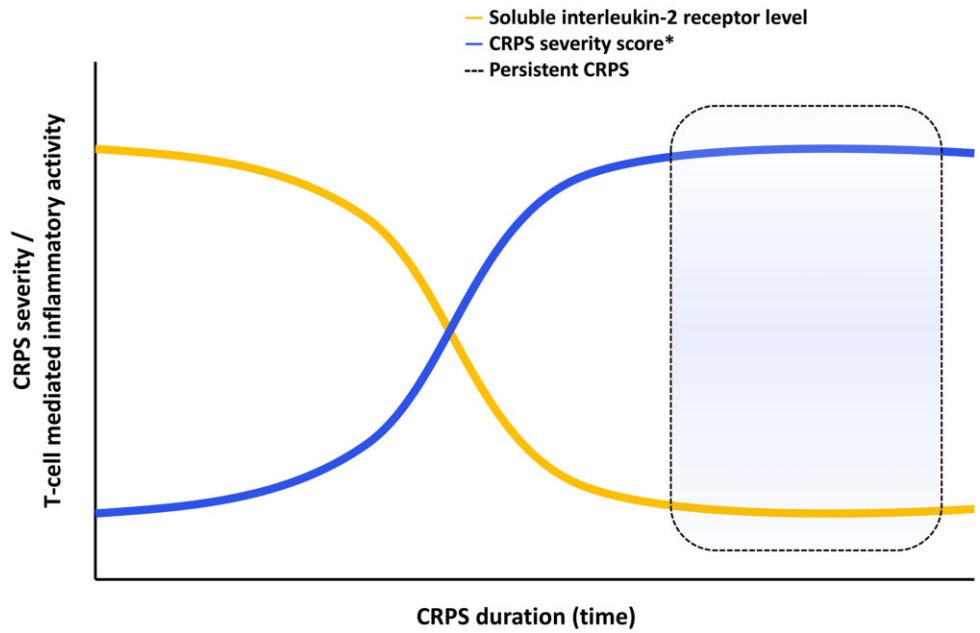

Figure 7. Hypothetical model of the relationship between inflammation involving T-cell activity and CRPS severity during the progression of CRPS.[26] In this model, T-cell activity is elevated during the onset and in the early phase of CRPS. As CRPS progresses, T-cell activity—and thus the serum soluble interleukin-2 receptor (sIL-2R) level—diminishes over time, while damage caused by this inflammatory activity—the CRPS syndrome severity—persists. Based on current understandings, post-traumatic inflammatory immune activation seems to be most prominent in early CRPS and seems to diminish as the syndrome progresses.[4,9,20,21,25] However, damage due to exaggerated inflammatory mechanisms may persist and possibly worsen due to other pathophysiological mechanisms such as central sensitization and vasomotor or motor disturbances gaining the upper hand.[4] In persistent CRPS, these other pathological mechanisms result in a (persistently) high syndrome severity.

CRPS severity score: In the CRPS severity score, several clinical signs and symptoms are scored and the sum of the score reflects the severity of CRPS.[6] Persistent CRPS= prolonged and intractable CRPS, usually >1 year after onset of CRPS.[5]

Abbreviations: CRPS = Complex Regional Pain Syndrome; sIL-2R = soluble Interleukin-2 receptor.

extremity.[2,3,20] In the transition from early to persistent CRPS, inflammatory mechanisms diminish.[4,20] In the persistent phase of CRPS, patients usually demonstrate a cold and blue or pale extremity that is less swollen.[20] Corresponding to the CRPS signs during the course of the syndrome, we suggest that in early warm CRPS, the T-cell activity is high and serum

sIL-2R levels are raised. Thereafter, when CRPS patients progress into the persistent subtype of CRPS, T-cell activation and thus serum sIL-2R levels will progressively decrease (Figure 6). Serum sIL-2R levels in persistent CRPS, and thus inflammation involving T-cell activity, will eventually normalize to a level comparable to healthy controls (Figure 6). Due to the damage caused by exaggerated inflammatory mechanisms and initiation of other pathophysiological mechanisms such as central sensitization and vasomotor or motor disturbances, the CRPS severity remains relatively high in persistent CRPS.[4] Of note, the assessed CRPS signs and symptoms in the CRPS severity score can change over time, but the sum-score of the CRPS severity score stays relatively high in persistent CRPS.

Although the observations above strengthen the notion that serum sIL-2R level may reflect the inflammation involving T-cell activity instead of the syndrome severity in patients with CRPS, our research group acknowledges that our model is still hypothetical and needs further research to be confirmed. To test our hypothetical model, it would be interesting to determine serial serum sIL-2R levels in a prospective multicenter cohort of early CRPS patients. These serial prospective measurements of serum sIL-2R levels are needed to investigate the activity of T cells during the course of the syndrome. Furthermore, it would be interesting to explore whether there are differences in the serum sIL-2R levels between different phenotypes of CRPS. The activity of T cells can be indicative for CRPS inflammatory syndrome activity and T-cell targeted therapies such as corticosteroids that should be started in a timely manner in CRPS.[4,27,28]

Conclusion

In a cohort of patients with persistent CRPS, T-cell mediated serum sIL-2R levels did not correlate with CRPS syndrome severity. Thus, serum sIL-2R levels cannot be used a biomarker to monitor syndrome severity in persistent CRPS. The role for serum sIL-2R in monitoring T-cell mediated syndrome activity is still to be established in a prospective cohort that follows early CRPS patients during the progression of CRPS.

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Data availability

The data used to support the findings of this study are restricted by the Medical Ethics Committee of Erasmus MC University Rotterdam and the General Data Protection Regulation of the EU in order to protect patient privacy.

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