



## Original Reports

## Preoperative Predictors of Complex Regional Pain Syndrome Outcomes in the 6 Months Following Total Knee Arthroplasty

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**Abstract:** This prospective observational study evaluated preoperative predictors of complex regional pain syndrome (CRPS) outcomes in the 6 months following total knee arthroplasty (TKA). Participants were n = 110 osteoarthritis patients (64.5% female) undergoing unilateral TKA with no prior CRPS history. Domains of negative affect (depression, anxiety, catastrophizing), pain (intensity, widespread pain, temporal summation of pain [TSP]), pain interference, sleep disturbance, and pro-inflammatory status (tumor necrosis factor-alpha [TNF- $\alpha$ ]) were assessed preoperatively. CRPS outcomes at 6-week and 6-month follow-up included the continuous CRPS Severity Score (CSS) and dichotomous CRPS diagnoses (2012 IASP criteria). At 6 months, 12.7% of participants met CRPS criteria, exhibiting a “warm CRPS” phenotype. Six-week CSS scores were predicted by greater preoperative depression, anxiety, catastrophizing, TSP, pain intensity, sleep disturbance, and TNF- $\alpha$  ( $P$ 's < .05). Provisional CRPS diagnosis at 6 weeks was predicted by higher preoperative TSP, sleep disturbance, and TNF- $\alpha$  ( $P$ 's < .05). CSS scores at 6 months were predicted by more widespread and intense preoperative pain, and higher preoperative TSP, pain interference, and TNF- $\alpha$  ( $P$ 's < .01). CRPS diagnosis at 6 months was predicted only by more widespread and intense pain preoperatively ( $P$ 's < .05). Risk for CRPS following TKA appears to involve preoperative central sensitization and inflammatory mechanisms. Preoperative negative affect is unlikely to directly influence long-term CRPS risk.

**Perspective:** This article identifies preoperative predictors of CRPS features at 6 months following total knee arthroplasty, including more widespread pain and higher pain intensity, temporal summation of pain, pain interference, and tumor necrosis factor-alpha levels. Findings suggest the importance of central sensitization and inflammatory mechanisms in CRPS risk following tissue trauma.

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**Key words:** Total knee arthroplasty, complex regional pain syndrome, inflammation, central sensitization, mechanisms.

Complex regional pain syndrome (CRPS) is a chronic pain condition typically beginning in a single limb that is characterized by spontaneous pain, allodynia and hyperalgesia, edema, changes in

skin temperature and color, altered sweating, and motor and trophic changes.<sup>7</sup> CRPS appears to have multiple interacting mechanisms, including central and peripheral sensitization, autonomic changes, enhanced

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inflammatory and immune activity, and altered limb representation in the brain.<sup>6,7</sup> Limited epidemiological work suggests CRPS disproportionately affects women and individuals in middle age,<sup>17,64</sup> and fracture and surgery appear to be 2 of the most common inciting events.<sup>17,31,35,64</sup> However, specific patient-level risk factors for CRPS following tissue trauma are not well understood. Identification of prospective risk factors for subsequent CRPS could help enhance understanding of CRPS risk mechanisms.

Clinical lore long held the belief that certain psychosocial characteristics, particularly elevated negative affect, increased risk for CRPS.<sup>6</sup> A comprehensive review of the cross-sectional research literature and at least one large prospective study of patients following fracture fail to support this clinical belief.<sup>2,3</sup> Nonetheless, a few prospective studies hint that psychological factors may be relevant for understanding mechanisms contributing to CRPS risk,<sup>20,34</sup> for example, via effects of negative affect-related catecholamine release on adrenergic CRPS mechanisms.<sup>6,7,36</sup> Additionally, some prospective studies suggest that CRPS, whether developing after fracture<sup>26,46,58</sup> or in the postsurgical setting,<sup>34,65</sup> may be predicted by elevated pain intensity prior to CRPS onset (surgery) or shortly after injury (fracture). This is consistent with the central sensitization mechanisms believed to be involved in CRPS,<sup>5,19,21,25,67</sup> and the likely role for central sensitization in driving elevated pain intensity prior to CRPS onset.<sup>48,76</sup> Consistent with the role of inflammation in established CRPS, particularly early CRPS,<sup>9,30,53,66</sup> numerous findings that CRPS is associated with elevated levels of pro-inflammatory cytokines (particularly tumor necrosis factor- $\alpha$ ; TNF- $\alpha$ )<sup>14,43,52,60,73,75</sup> suggest that pro-inflammatory status could be another CRPS risk mechanism. Finally, female sex may increase risk of CRPS following injury.<sup>46,63</sup> In sum, while a few longitudinal studies have identified individual risk factors for CRPS, prior prospective work has not evaluated a comprehensive set of biopsychosocial factors that may increase CRPS risk following tissue trauma, despite the potential value for understanding mechanisms contributing to CRPS risk.

Although whether CRPS occurs following total knee arthroplasty (TKA) remains debated by some,<sup>50</sup> 2 prior studies using standardized diagnostic criteria have reported a CRPS incidence of up to 12% at 6 months following TKA.<sup>34,41</sup> The current project therefore used TKA as a model to prospectively test a comprehensive set of preoperative predictors of CRPS outcomes in the 6 months following TKA. The predictors tested addressed the domains of pain (pain intensity, extent of widespread pain, temporal summation of pain), negative affect (depression, anxiety, catastrophizing), sleep disturbance, function (pain interference), and pro-inflammatory status (TNF- $\alpha$ ). We hypothesized that elevated levels on all of these preoperative measures would be associated longitudinally with higher levels of CRPS features and greater risk of meeting CRPS diagnostic criteria at 6-week and 6-month post-TKA follow-up.

## Methods

### Design

The current study used a mixed between/within-subjects longitudinal design that included assessment of pain, psychosocial phenotype measures, and cytokines at preoperative baseline, and assessment of CRPS-related outcome measures at 6-week and 6-month post-TKA follow-up. The current dataset is part of a larger project examining perioperative oxidative stress mechanisms of post-TKA pain (described elsewhere<sup>10</sup>).

### Participants

Participants were individuals of both sexes, age 55 or greater, and scheduled to undergo unilateral TKA for treatment of degenerative knee joint changes and pain related to chronic osteoarthritis. Participants were recruited from the practices of the 2 orthopedic surgeon coauthors (G.P. and A.S.) at Vanderbilt University Medical Center (VUMC). Recruitment was primarily carried out via in-person introductory presentations during a required pre-operative TKA education session by the research coordinator in accordance with IRB requirements. To address COVID-related changes in clinical procedures affecting later enrollees, some individuals were recruited via telephone calls by the research coordinator to patients scheduled to undergo TKA. Interested individuals were provided with study information, and if interested, were screened for eligibility, and then provided informed consent. All study procedures were approved by the VUMC Institutional Review Board. All participants were enrolled between August 2017 and June 2021. The targeted sample size ( $n = 120$ ) for the parent study was determined based on a power analysis indicating that this sample size would lead to  $>.80$  power to detect associations between the oxidative stress measure (F2-isoprostanes) that was the primary focus of the project and continuous pain and CRPS outcomes.

Inclusion criteria for study participation were: 1) intact cognitive status and ability to provide informed consent (based on a Mini Mental State Examination score  $\geq 24$ ),<sup>28</sup> 2) ability to read and write in English sufficiently to understand and complete study questionnaires, 3) age 55 years or older, 4) undergoing unilateral TKA, and 5) medical diagnosis of osteoarthritis. Exclusion criteria were: 1) a diagnosis of CRPS prior to undergoing TKA (by history or in the electronic health record), 2) undergoing TKA revision, 3) presence of lower extremity vascular disease, inflammatory or autoimmune disorders, or malignancy, and 4) presence of other medical conditions that in the opinion of the orthopedic surgeons would make a participant's study participation unsafe. Participants received \$200 for completing the full study.

The pool of potential participants (ie, individuals attending the TKA education classes) was  $n = 985$ , and  $n = 303$  were interested in the study and screened. Of

**Table 1. Preoperative Demographic Characteristics and Predictors, and CRPS Outcomes at Follow-Up**

	MEDIAN (IQR) OR N (%) (N = 110)
Demographic characteristics:	
Age (years)	68.0 (9.0)
Gender (% female)	71 (64.5)
Race/Ethnicity:	
Non-Hispanic White	106 (96.4)
African-American	4 (3.6)
BMI	30.9 (7.6)
Diabetes	22 (20.0)
Preoperative predictors:	
CES-D	18.0 (10.0)
CATS	12.0 (15.0)
STAI	30.0 (10.0)
MBM	4.0 (4.0)
TSP	2.0 (2.0)
MPQ-2	1.8 (2.23)
PROMIS Interf	62.1 (8.8)
PROMIS Sleep	53.3 (13.1)
TNF- $\alpha$ (pg/mL)	1.49 (0.52)
CRPS diagnostic outcomes:	
Provisional CRPS diagnosis at 6-week FU	69 (62.7)
CRPS diagnosis at 6-month FU	14 (12.7)

Abbreviations: CES-D, Center for Epidemiological Studies-Depression Scale; CATS, Catastrophizing Scale; STAI, State Trait Anxiety Inventory; MBM, Michigan Body Map; TSP, Temporal Summation of Pain; MPQ-2, McGill Pain Questionnaire-Short Form 2; PROMIS Interf, PROMIS Pain Interference (T score); PROMIS Sleep, PROMIS Sleep Disturbance (T Score); TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; FU, Follow-Up.

these,  $n = 120$  consented, with  $n = 7$  subsequently failing screening (cognitive dysfunction, medical exclusions). The final sample was  $n = 113$  (no participants withdrew or were lost to follow-up), with the final analyzed sample including all participants ( $n = 110$ ) with data available regarding CRPS diagnosis at 6-month follow-up ( $n = 3$  were missing data due to inability to carry out in person follow-up evaluations due to COVID-related study restrictions). Preoperative participant demographics are summarized in Table 1. The sample consisted of older adults who were primarily of non-Hispanic white race/ethnicity, and nearly two-thirds of the sample were female.

## Psychometric Measures

### Pain

Knee pain over the week preceding the preoperative assessment was assessed using the Short Form-McGill Pain Questionnaire 2 (MPQ-2).<sup>22,23</sup> For purposes of the current study, only the MPQ-2 Total score was examined (0-10 scale). Participants additionally completed the Michigan Body Map (MBM), a validated measure that was used to assess the number of body regions in which persistent or recurrent pain was experienced in the 90 days preceding the preoperative assessment.<sup>11</sup> An 11-point NRS anchored

with "no pain" and "worst possible pain" was also used to rate worst knee pain in the 24 hours preceding CRPS assessment at 6-month follow-up.<sup>47</sup>

### Psychosocial Status

Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale (CES-D; 20 item version), a widely used standardized measure of depressive symptoms validated for use in older populations.<sup>4,38</sup> The trait form of the State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms,<sup>70</sup> with higher scores indicating greater tendency to experience anxiety symptoms. Pain catastrophizing was assessed using the Pain Catastrophizing Scale (PCS),<sup>71</sup> a measure assessing the degree to which individuals have negative thoughts and feelings when experiencing pain.

### Sleep Disturbance

Sleep disturbance was assessed using the PROMIS Sleep Disturbance – Short Form 8a, an instrument assessing sleep quality, sleep depth, and restoration associated with sleep over the past week.<sup>77</sup>

### Function

The PROMIS Short Form v1.0 - Pain Interference 8a scale (PROMIS Interference) was used to assess pain-related life interference over the past week.<sup>1,62</sup>

## Assessment of Temporal Summation of Pain

Temporal summation of pain (TSP) is believed to be an index of enhanced spinal responsiveness to nociceptive stimuli (ie, central sensitization).<sup>24</sup> Elevated TSP has been reported previously in osteoarthritis samples similar to participants in the present work.<sup>37,59</sup> TSP to punctate mechanical stimuli was assessed using procedures based on Goodin et al.<sup>29</sup> The stimulus used was a 100g monofilament, with this stimulus weight determined based on weights shown to elicit TSP in prior literature (eg, ranging from 25 g to 300 g).<sup>29,51</sup> A single stimulus was first applied for one second to the affected knee (4cm above the patella, 8 cm toward the midline), with pain intensity rated using a 0-10 NRS (anchored with "no pain" and "worst possible pain"). Then, using the same procedures as above, a series of 10 punctate stimuli were delivered at a rate of one stimulus per second to the affected knee, with an NRS pain intensity rating then obtained to describe the highest pain intensity experienced. This procedure was repeated twice. The change in pain intensity between the first stimulus and the stimulus eliciting the highest pain rating (mean of the 2 trials) was used to index preoperative TSP in the affected knee (larger positive values indicated greater TSP).

## Assessment of CRPS

To ensure standardized assessment of CRPS signs and symptoms, a CRPS database checklist like that used in our past multisite research was used.<sup>31,32</sup> This checklist presented a complete list of the signs and symptoms used to diagnose CRPS according to the 2012 IASP criteria (ie, Budapest clinical criteria).<sup>32</sup> All assessments were conducted by a single research coordinator (S.A.) based on written standardized procedures used in prior work.<sup>32</sup> This individual also underwent thorough in-person training in CRPS assessment conducted by a CRPS expert (R.N.H.). Objective temperature asymmetry between the affected and unaffected sides was assessed via infrared thermometry conducted 8 cm toward midline at the level of the top and bottom of the incision (2 readings at each location on each leg, all averaged), with an average bilateral asymmetry of 1.5°C or greater used as the criterion for asymmetric temperature. No attempt was made to distinguish between CRPS-Type I versus Type II subtypes, given that diagnostic features are identical between the 2.

To optimize statistical power for prediction of CRPS-related outcomes, the continuous CRPS Severity Score (CSS) was used.<sup>33,35</sup> The CSS was scored according to previously published procedures.<sup>35</sup> In brief, the CSS was calculated by summing the responses indicating presence/absence (coded 1/0) of each sign and symptom as recorded on the CRPS database checklist. The CSS therefore provides a continuous index of the extent of CRPS diagnostic signs and symptoms. The potential range of CSS scores was 0-16.

Based on prior work indicating that early CRPS is characterized predominantly by inflammatory features which may remit to an extent over time, we also calculated the Inflammatory Index as described in Bruehl et al<sup>9</sup> as a supplementary CRPS outcome. This index represented a sum (ranging from 0 to 6) of dichotomous values (coded 1/0 for present/absent) for 3 symptoms and 3 signs indicative of inflammation (red skin color, warmer skin temperature, and edema on the affected side, ie, rubor, calor, and tumor as described in classical inflammation).

Finally, dichotomous CRPS diagnosis at 6-week and 6-month follow-up was determined for each participant based upon meeting the 2012 IASP symptom and sign criteria (ie, at least 3 of 4 symptom categories positive and at least 2 of 4 sign categories positive).<sup>32</sup> "Pain disproportionate to the inciting event" was not explicitly required for diagnosis for 2 reasons. First, at the 6-week follow-up, disproportionate pain was difficult to judge due to the possibility of ongoing tissue healing secondary to the TKA procedure. CRPS diagnostic status at this early follow-up should be considered provisional only, due to the possibility that CRPS features reflect delayed healing that will resolve and the fact that diagnostic criteria exclude a CRPS diagnosis if diagnostic symptoms can be attributed to another condition (ie, ongoing postsurgical healing). Second, it was assumed that any significant ongoing pain 6 months following TKA

would be considered disproportionate given that the TKA procedure had corrected the underlying osteoarthritis pain generator and acute healing should be largely resolved. Although CRPS diagnostic outcomes are less statistically powerful due to their dichotomous nature, they were judged to be valuable for generalizing results to the clinical CRPS population.

## Assessment of Inflammatory Cytokines

Systemic levels of pro-inflammatory cytokines were assessed using a Meso Scale Diagnostics V-Plex Human Pro-inflammatory Panel employing electrochemiluminescent detection (Meso Scale Diagnostics, Rockville, MD). The current study focused on systemic levels of TNF- $\alpha$  as a biological indicator of pre-operative pro-inflammatory status and potential risk mechanism for CRPS.<sup>40,43,45,61,79</sup> Plasma samples (described below) were analyzed in duplicate and assays were performed per manufacturer protocol and read and analyzed on a QuickPlex SQ120 (Meso Scale Diagnostics, Rockville, MD). Assay results are expressed as the mean of these duplicate assays (in pg/mL). The decision to obtain blood samples for cytokine assays was not made until after the study was ongoing, and these samples were therefore available for only  $n = 72$  participants.

## Procedure

After providing informed consent, a baseline preoperative assessment session was carried out by a research coordinator in the participant's home shortly before the scheduled surgery date (median = 3.0 days prior to surgery). The assessment session included completion of a demographic questionnaire and the measures of pain, psychosocial status, and function described above, as well as assessment of TSP.

The anesthesia and postoperative care protocol is described in supplemental materials (Supplement 1). Blood draws for cytokine assays were performed on the day of TKA surgery in the operating room from the clinically placed intravenous catheter. We collected 8 mL of blood after induction of anesthesia, but prior to incision or placement of the lower extremity tourniquet. Blood was drawn into anticoagulant EDTA tubes (lavender caps) with glutathione and butylated hydroxytoluene added. Samples were then immediately stored on ice, and quickly transported to the laboratory, centrifuged at 1000G at 4°C for 10 minutes, and plasma separated and stored in a cryovial at -80°C until analyzed as described above.

At 6 weeks (6-8 week window) and 6 months (24-28 week window) following the TKA procedure, the research coordinator conducted a follow-up assessment session in the participant's home. During these follow-up sessions, a CRPS assessment was conducted using the CRPS database form and standardized procedures previously described.

## Statistical Analysis

All statistical analyses were conducted using SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY). Participant demographics, preoperative pain and psychosocial measures, pre-operative levels of systemic TNF- $\alpha$ , and CRPS outcomes at both follow-ups are summarized in Table 1 using either percentages or medians (IQR). Nonparametric Spearman correlations were used to characterize unadjusted (zero-order) associations among the predictors evaluated and between potential predictors and CRPS outcomes at follow-up. To examine longitudinal associations between the hypothesized preoperative predictors and CRPS status at 6-week and 6-month post-TKA follow-up, we used generalized linear models (GLM). Inspection of the distributions of the CSS and Inflammation Index outcomes indicated that they were significantly non-normal (Kolmogorov-Smirnov tests, all  $P$ 's < .005). Both outcomes were a good fit with a Poisson distribution (all  $P$ 's > .27), so GLM analyses of these outcomes specified a Poisson distribution. GLM analyses of dichotomous CRPS diagnoses specified a binomial distribution. To reduce the potential for confounding, we controlled for participant age, sex, and body mass index (BMI) in each model. Unlike some prior work, female sex was not associated with CRPS measures in any model (all  $P$ 's > .35; details not reported). TNF- $\alpha$  levels were right-skewed in our data, so we conservatively applied log base 2 transformations to this measure prior to including it in analyses. We used a 2-sided  $P$  < .05 significance level to define statistical significance.

## Results

### CRPS Outcomes Following TKA

At the early 6-week follow-up assessment, a clinical presentation meeting CRPS diagnostic criteria was noted in 69 of 110 participants (62.7%). In most, this presentation was likely attributable to the effects of ongoing acute healing and would not merit a clinical diagnosis of CRPS, so this diagnosis is considered provisional. Among the  $n = 69$  participants meriting a provisional CRPS diagnosis at 6 weeks,  $n = 10$  (14.5%) continued to meet CRPS criteria at 6-month follow-up. An additional  $n = 4$  participants not meeting CRPS criteria at 6 weeks did meet criteria at 6-month follow-up. For the sample as a whole, the incidence of CRPS based on meeting diagnostic criteria at 6-month follow-up was 12.7% (14 of 110 participants).

Table 2 summarizes the characteristic features of CRPS in participants meeting versus not meeting CRPS criteria at 6-week (provisional CRPS) and 6-month follow-up. Given the higher confidence in CRPS diagnosis at 6 months post-TKA, only results for this timepoint are discussed below. Relative to participants not meeting CRPS criteria at 6 months, those experiencing CRPS were characterized by significantly more allodynia/hyperalgesia, temperature asymmetry (90% were warmer on the affected side), skin color asymmetry (with 50% displaying red skin color), sweating asymmetry, edema in the affected limb, and motor changes. Although worst pain intensity in the past 24 hours was significantly higher (3 times as high) in the CRPS group than in the non-CRPS group ( $P$  < .01), pain intensity was in the mild-moderate range for most (eg, only  $n = 6$  participants

**Table 2. CRPS Diagnostic Features by CRPS Status at Follow-Up**

CRPS DIAGNOSTIC FEATURES	6-WEEK FOLLOW-UP		6-MONTH FOLLOW-UP	
	NON-CRPS (N = 41)	PROVISIONAL CRPS (N = 69)	NON-CRPS (N = 96)	CRPS (N = 14)
Self-reported symptoms (% Yes):				
Allodynia or hyperalgesia	27.5	53.6**	13.5	64.3***
Temperature asymmetry	40.0	88.4***	16.7	71.4***
Skin color asymmetry	17.5	55.1***	3.1	28.6***
Sweating asymmetry	0.0	1.4	0.0	7.1**
Asymmetric edema	47.5	94.2***	27.1	71.4***
Trophic changes	5.0	8.7	8.3	14.3
Motor changes	65.0	97.1***	43.8	100.0***
Signs observed on exam (% Yes):				
Hyperalgesia to pinprick	13.2	17.4	2.3	14.3*
Allodynia	17.9	29.0	8.0	21.4
Temperature asymmetry	59.0	92.8***	33.7	71.4**
Skin color asymmetry	5.1	52.2***	4.6	14.3
Sweating asymmetry	0.0	1.4	0.0	0.0
Asymmetric edema	56.4	87.0***	44.8	78.6*
Trophic changes	2.6	13.0	6.9	14.3
Motor changes	28.2	59.4**	13.8	57.1***
CSS (median, IQR)	4.0 (2.0)	7.0 (3.0)***	2.0 (3.0)	6.0 (3.0)***
Inflammation index (median, IQR)	2.0 (2.0)	4.0 (1.0)***	2.0 (1.0)	3.0 (2.0)***
NRS past 24-hour worst pain (median, IQR)	2.0 (3.0)	4.0 (3.0)*	1.0 (2.0)	3.0 (4.0)**

Abbreviations: CSS, CRPS Severity Score; NRS, numeric rating scale.

\* $P$  < .05

\*\* $P$  < .01.

\*\*\* $P$  < .001.

reported worst pain intensity ranging from 4/10-8/10). As expected, CSS values in the CRPS group (Median = 6; range 5-10) were significantly higher ( $P < .001$ ) at 6-month follow-up than in the non-CRPS group (Median = 2; range 0-6). The CRPS group also displayed significantly higher ( $P < .001$ ) scores on the Inflammation Index at 6-month follow-up (Median = 3; range = 1-5) than did the non-CRPS group (Median = 2; range = 0-3).

### Zero-Order Correlations

Table 3 presents zero-order Spearman's nonparametric correlations among the preoperative predictors evaluated. Unsurprisingly, negative affect-related constructs (depression, anxiety, catastrophizing) showed large intercorrelations. These constructs also showed generally large positive associations with pain intensity, pain interference, and sleep disturbance, although associations were somewhat smaller for anxiety. Extent of widespread pain showed small but significant positive associations with pain intensity, as well as anxiety, catastrophizing, and pain interference. Similarly, TSP displayed its largest (positive) association with pain intensity, but was also significantly associated positively with depression, catastrophizing, and sleep disturbance. Sleep disturbance was positively associated not only with negative affect as noted above, but also with pain intensity and interference. Finally, greater TNF- $\alpha$  levels were associated significantly only with higher depression levels.

Table 4 presents zero-order (unadjusted) Spearman's nonparametric correlations between hypothesized preoperative predictors and CRPS-related outcome measures at follow-up. Higher scores on the CSS (a continuous measure of CRPS-related clinical features) at 6-week follow-up were associated with significantly higher preoperative baseline levels of depression, catastrophizing, trait anxiety, TSP, pain intensity (MPQ-2), and sleep disturbance. A similar positive association between preoperative TNF- $\alpha$  levels and CSS scores at 6 weeks approached significance as well. Higher preoperative depression, TSP, pain intensity, and sleep disturbance were also specifically associated with a significantly greater number of

inflammatory features (Inflammation Index) at this early follow-up. Only elevated TSP and preoperative pain intensity were significantly associated with greater likelihood of a dichotomous provisional CRPS diagnosis at 6 weeks, with a similar nonsignificant trend for TNF- $\alpha$ .

Greater CSS scores as 6-month follow-up were associated significantly only with higher preoperative levels of TSP and pain intensity, although a similar nonsignificant trend for catastrophizing was noted. Higher preoperative pain intensity also was significantly associated with extent of inflammatory features at 6-month follow-up. A similar trend for TNF- $\alpha$  approached significance as well. Meeting CRPS diagnostic criteria at 6-month follow-up was significantly associated only with elevated preoperative pain intensity, although a similar nonsignificant trend for extent of recent widespread pain (MBM) was noted.

### Preoperative Predictors of Continuous CSS Outcomes at Postoperative Follow-Up

GLM analyses (Poisson distribution) revealed numerous preoperative baseline predictors of CSS scores at 6-week follow-up when potential confounding influences of age, sex, and BMI were statistically controlled (Table 5). Greater preoperative levels of depression, catastrophizing, trait anxiety, TSP, pain intensity, sleep disturbance, and TNF- $\alpha$  were all significant prospective predictors of higher CSS scores at 6-week follow-up.

Similar GLM analyses revealed a number of preoperative baseline predictors of CSS scores at 6-month follow-up when potential confounds were statistically controlled. More widespread pain preoperatively (MBM) and higher preoperative levels of TSP, pain intensity, pain interference, and TNF- $\alpha$  were all significant prospective predictors of higher CSS scores at 6-month follow-up. In terms of specific inflammatory features at 6 months post-TKA, GLMs indicated that elevated preoperative pain intensity and pro-inflammatory status (TNF- $\alpha$ ) both prospectively predicted higher Inflammation Index values at 6-month follow-up.

**Table 3. Zero-Order Spearman's Nonparametric Correlations Among Preoperative Predictors**

PREOPERATIVE PREDICTOR	CES-D	CATS	STAI	MBM	TSP	MPQ-2	PROMIS INTERF	PROMIS SLEEP
CATS	0.66***	—	—	—	—	—	—	—
STAI	0.53***	0.60***	—	—	—	—	—	—
MBM	0.14	0.21*	0.21*	—	—	—	—	—
TSP	0.28**	0.29**	0.13	0.15	—	—	—	—
MPQ-2	0.57***	0.60***	0.20*	0.24*	0.30**	—	—	—
PROMIS Interf	0.52***	0.62***	0.37***	0.22*	0.12	0.56***	—	—
PROMIS Sleep	0.52***	0.42***	0.38***	0.18 <sup>†</sup>	0.20*	0.39***	0.38***	—
TNF- $\alpha$	0.26*	0.19	0.12	0.19	0.08	0.09	0.13	0.17

Abbreviations: CES-D, Center for Epidemiological Studies-Depression Scale; CATS, Catastrophizing Scale; STAI, State Trait Anxiety Inventory; MBM, Michigan Body Map; TSP, Temporal Summation of Pain; MPQ-2, McGill Pain Questionnaire-Short Form 2; PROMIS Interf, PROMIS Pain Interference (T score); PROMIS Sleep, PROMIS Sleep Disturbance (T Score); TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

<sup>†</sup> $P < .10$ .

\* $P < .05$ .

\*\* $P < .01$ .

\*\*\* $P < .001$ .

**Table 4. Zero-Order Spearman's Nonparametric Correlations Between Preoperative Predictors and CRPS-Related Outcome Measures at Follow-Up**

PREOPERATIVE PREDICTOR	CSS 6-		INFLAMMATION		PROVISIONAL	
	WEEK FU	MONTH FU	INDEX 6-WEEK FU	INDEX 6-MONTH FU	CRPS DIAGNOSIS 6-WEEK FU	CRPS DIAGNOSIS 6-MONTH FU
CES-D	0.20*	0.10	0.22*	0.14	0.08	0.03
CATS	0.20*	0.17 <sup>†</sup>	0.16	0.10	0.10	0.01
STAI	0.19*	0.08	0.12	0.05	0.12	-0.01
MBM	0.04	0.16	-0.04	-0.12	0.00	0.17 <sup>†</sup>
TSP	0.25**	0.22*	0.25**	0.10	0.27**	0.12
MPQ-2	0.27**	0.42***	0.20*	0.27**	0.15	0.20*
PROMIS Interf	0.12	0.07	0.11	-0.08	0.00	-0.05
PROMIS Sleep	0.34***	0.17	0.30**	0.12	0.23*	0.03
TNF-a	0.20 <sup>†</sup>	0.16	0.09	0.22 <sup>†</sup>	0.20 <sup>†</sup>	0.02

Abbreviations: CES-D, Center for Epidemiological Studies-Depression Scale; CATS, Catastrophizing Scale; STAI, State Trait Anxiety Inventory; MBM, Michigan Body Map; TSP, Temporal Summation of Pain; MPQ-2, McGill Pain Questionnaire-Short Form 2; PROMIS Interf, PROMIS Pain Interference (T score); PROMIS Sleep, PROMIS Sleep Disturbance (T Score); TNF-a, tumor necrosis factor-alpha; CSS, CRPS Severity Score; FU, Follow-Up.

NOTE: Correlations for dichotomous CRPS diagnostic outcomes are the equivalent of point-biserial correlations.

<sup>†</sup> $P < .10$ .

\* $P < .05$ .

\*\* $P < .01$ .

\*\*\* $P < .001$ .

### Preoperative Predictors of Dichotomous CRPS Diagnosis at Postoperative Follow-Up

GLM analyses (binomial distribution) revealed that when controlling for potential confounding influences of age, sex, and BMI, elevated preoperative sleep disturbance as well as greater preoperative TSP and pro-inflammatory status (TNF-a) were each significant predictors of a provisional CRPS diagnosis at 6-week follow-up (Table 5). To quantify the predictive value of these measures in terms of diagnostic accuracy, we conducted exploratory analyses using Receiver Operating Characteristic curve analysis procedures, with the area under the curve (c-index) used as the model accuracy criterion. A c-index of 0.50 indicates chance prediction, with a c-index of 0.70 typically considered a good predictive model (ie, 70% of cases classified correctly). None of the individual predictors showed good accuracy for predicting CRPS diagnosis at 6 weeks (Sleep Disturbance = 0.64, TSP = 0.66, TNF-a = 0.61). After appropriate Z transformations for each individual measure, combined predictors were then evaluated for comparison to the univariate models. The combination of sleep disturbance and TSP led to a modest increase in predictive accuracy (an additional 3% of cases classified accurately) beyond the best single predictor, TSP (c-index = 0.69). The addition of TNF-a to this combined model notably increased the percentage of cases classified correctly (an additional 8%) and led to a good predictive model (c-index = 0.77).

GLM analyses similar to those above regarding longer-term CRPS outcomes indicated that only more widespread pain preoperatively (MBM) and elevated preoperative pain intensity were significant predictors of dichotomous CRPS diagnosis at 6-month follow-up (Table 5). In ROC analyses, inspection of c-index values indicated that none of the individual predictors showed good accuracy for predicting CRPS diagnosis at 6 months,

although preoperative pain intensity approached this criterion (MBM = 0.62, pain intensity = 0.68). The combination of these 2 measures (Z-transformed) produced little increase in predictive accuracy (an additional 1% of cases classified accurately; c-index = 0.69) beyond the best single predictor, pain intensity.

### Discussion

Relatively few longitudinal studies have evaluated risk factors for CRPS, with all focusing on a narrow range of predictors.<sup>2,20,27,34,46,58,65</sup> We examined a more comprehensive set of preoperative biopsychosocial risk factors regarding prospective associations with CRPS-related outcomes with the goal of enhancing understanding of CRPS risk mechanisms. CRPS outcomes at 6 months post-TKA most clearly reflect the clinical condition of CRPS, because by this point it is difficult to attribute ongoing CRPS-related features to acute healing. Results revealed a number of preoperative predictors of extent of CRPS clinical features (CSS scores) at 6-month follow-up, including more widespread preoperative pain and higher preoperative pain intensity and pain interference, higher temporal summation of pain (TSP), and higher levels of the pro-inflammatory cytokine TNF-a. Less statistically powerful analyses of CRPS diagnostic status at 6-month follow-up indicated that only presence of more widespread and more intense pain preoperatively were significant predictors. Incidence of CRPS based on the 2012 IASP criteria at 6 months postoperatively in the current study (12.7%) was quite similar to 6-month CRPS incidence in 2 prior TKA studies.<sup>34,41</sup>

Viewed within a mechanistic context, our results suggest that elevated preoperative levels of central sensitization and inflammation may identify patients likely to experience more extensive CRPS-related features 6 months following TKA. Central sensitization

Table 5. GLM Analyses of Prospective Preoperative Predictors of CRPS-Related Outcome Measures at Follow-Up.

PREOPERATIVE PREDICTOR	6-WEEK FOLLOW-UP						6-MONTH FOLLOW-UP											
	CSS			INFLAMMATION INDEX			PROVISIONAL CRPS DIAGNOSIS			CSS			INFLAMMATION INDEX			CRPS DIAGNOSIS		
	BETA	SE	P VALUE	BETA	SE	P VALUE	BETA	SE	P VALUE	BETA	SE	P VALUE	BETA	SE	P VALUE	BETA	SE	P VALUE
CES-D	0.011	0.006	.043	0.010	0.007	.153	0.016	0.029	.573	0.007	0.008	.365	0.007	0.010	.499	0.010	0.042	.801
CATS	0.009	0.003	.011	0.006	0.004	.164	0.021	0.019	.268	0.007	0.005	.128	0.005	0.007	.472	0.006	0.026	.821
STAI	0.008	0.004	.032	0.006	0.005	.266	0.024	0.024	.304	0.003	0.006	.636	0.002	0.008	.811	0.000	0.031	.996
MBM	0.015	0.010	.158	0.004	0.014	.770	0.052	0.061	.389	0.040	0.015	.005	-0.007	0.022	.749	0.202	0.076	.008
TSP	0.072	0.028	.009	0.064	0.036	.081	0.473	0.174	.007	0.113	0.040	.005	0.030	0.053	.572	0.238	0.208	.253
MPQ-2	0.055	0.021	.010	0.042	0.028	.141	0.190	0.125	.130	0.148	0.030	<.001	0.092	0.041	.023	0.362	0.160	.023
PROMIS Interf	0.007	0.006	.174	0.008	0.007	.255	0.018	0.028	.515	0.043	0.007	<.001	-0.001	0.010	.942	0.006	0.040	.879
PROMIS Sleep	0.014	0.004	.001	0.013	0.006	.018	0.068	0.026	.007	0.011	0.006	.075	0.008	0.008	.358	0.014	0.032	.663
TNF-a	0.219	0.083	.009	0.138	0.111	.214	1.462	0.642	.023	0.375	0.118	.001	0.322	0.154	.036	0.764	0.642	.234

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CATS, Catastrophizing Scale; STAI, State Trait Anxiety Inventory; MBM, Michigan Body Map; TSP, Temporal Summation of Pain; MPQ-2, McGill Pain Questionnaire-Short Form 2; PROMIS Interf, PROMIS Pain Interference (T score); PROMIS Sleep, PROMIS Sleep Disturbance (T score); TNF-a, tumor necrosis factor-alpha; CSS, CRPS Severity Score.  
 NOTE: Analyses of continuous CSS and Inflammation Index outcomes specified a binomial distribution. Analyses of dichotomous CRPS diagnostic outcomes specified a binomial distribution. TNF-a values were log2 transformed to reduce the impact of outliers. Significant results are highlighted in bold text.

mechanisms are supported by the predictive utility of more intense and widespread pain preoperatively, both of which are linked to central sensitization.<sup>16,39,68,76,78</sup> Our findings are entirely consistent with previous prospective studies reporting that elevated pain intensity pre-surgery or shortly after injury predicts subsequent CRPS.<sup>26,34,46,58,65</sup> Intriguingly, results of one recent large retrospective electronic health record study suggested that presence of fibromyalgia, a condition characterized by widespread pain, may be a risk factor for CRPS.<sup>55</sup> Findings that preoperative TSP predicts CRPS features at follow-up more directly argue for involvement of central sensitization in CRPS risk, given that TSP is an accepted laboratory index of central sensitization.<sup>24</sup> The importance of central sensitization mechanisms is further supported by prior work indicating that central sensitization is detectable in patients once CRPS is established.<sup>25,67</sup> Although central sensitization mechanisms are implicated in the current findings, prior work in osteoarthritis patients<sup>15,56</sup> suggests that elevated preoperative pain intensity in the current sample could also in part reflect peripheral sensitization mechanisms known to be involved in CRPS.<sup>74</sup> Finally, findings that more widespread and intense pain preoperatively not only predict extent of CRPS features but also predict dichotomous CRPS diagnosis at 6 months post-TKA further highlight the importance of central sensitization mechanisms in CRPS risk.

The present study also found that higher preoperative levels of TNF-a, a key pro-inflammatory cytokine, predict extent of CRPS clinical features at 6-month follow-up. This supports involvement of preoperative pro-inflammatory status in CRPS risk post-TKA. Notably, TNF-a was not associated with any pain phenotype variables at preoperative baseline, suggesting that CRPS predictive effects of this inflammatory marker were not simply due to baseline associations carrying forward to follow-up. Clinical relevance of these TNF-a findings to CRPS is highlighted by findings that anti-TNF-a interventions reduce CRPS symptoms.<sup>26,44</sup> A role for preoperative inflammatory status in CRPS risk is also consistent with prior work suggesting involvement of the nfKappaB pathway in CRPS risk,<sup>18,42</sup> mechanistic links between nfKappaB activation and pro-inflammatory cytokine release,<sup>42,72</sup> and evidence that CRPS following traumatic injury is related to differential DNA methylation in immune and inflammatory pathways.<sup>8</sup>

Results at 6-week follow-up, when CRPS diagnosis is only provisional due to ongoing acute healing, revealed an even larger set of predictors. Elevated preoperative pain intensity, TSP, and TNF-a levels again predicted greater extent of CRPS features at 6 weeks. Elevated depression, anxiety, catastrophizing, and sleep disturbance also predicted extent of CRPS features at 6 weeks. In terms of CRPS mechanisms, psychosocial features such as depression and anxiety may capture negative affect-related catecholaminergic activity<sup>12,36,54</sup> that could interact with known autonomic mechanisms of CRPS as in proposed theoretical models.<sup>6,7</sup> For the less statistically powerful test predicting provisional dichotomous CRPS diagnosis at 6 weeks, elevated TSP, sleep

disturbance, and TNF- $\alpha$  levels preoperatively all were significant longitudinal predictors. Similar to findings at 6-month follow-up, these results suggest a role for central sensitization (TSP) and inflammatory mechanisms (TNF- $\alpha$ ) as risk factors for early postsurgical emergence of CRPS-related phenomena.

Considering the pattern of predictors of CRPS features at shorter versus longer-term follow-up, it is notable that while preoperative negative affect-related measures were predictors of CRPS features at 6 weeks, they were not predictors at 6 months. This is consistent with findings of one previous study examining CRPS post-TKA, which indicated that anxiety predicted meeting CRPS criteria at 1 month but not 6-month follow-up.<sup>34</sup> At 4-6 weeks postoperatively, CRPS is only a provisional diagnosis due to ongoing acute healing. Absence of predictive effects at 6-month follow-up in this and other prior TKA work, as well as negative findings in one large prospective post-fracture study,<sup>2</sup> indicate that negative affect is unlikely to be a risk factor for longer-term CRPS diagnosis.

One finding suggested that sleep disturbance may be a relevant but overlooked issue in understanding CRPS. At 6-week follow-up, only preoperative sleep disturbance predicted extent of inflammatory signs and symptoms, features contributing heavily to CRPS diagnosis at this time point. Such associations are consistent with recent work suggesting that sleep disturbance is associated with a pro-inflammatory state.<sup>13,57,69</sup> The current results indicate that sleep disturbance may warrant systematic evaluation in future CRPS studies. In contrast to the early follow-up period, extent of inflammatory features at 6 months was predicted only by preoperative pain intensity and TNF- $\alpha$  levels. Such findings are consistent with predictive results for CRPS-specific outcomes, again suggesting the potential importance of preoperative central sensitization and pro-inflammatory status.

Additional prospective work to replicate and generalize the current findings to other relevant populations (eg, carpal tunnel surgery, fracture) is necessary. Although predictive model development was not the purpose of this study, the current results could help guide development of optimized clinical predictive algorithms. For example, inspection of the pattern of intercorrelations between predictors suggests some independence among the 3 variables predicting provisional CRPS diagnosis at 6 weeks (sleep disturbance, TSP, and TNF- $\alpha$ ), with the largest proportion of shared variance between sleep disturbance and TSP (4%) and the lowest between TSP and TNF- $\alpha$  (<1%). The potential impact of differing overlapping variance on predictive models can be seen through inspection of c-index values for various models. The addition of TNF- $\alpha$  to a combined model increased accuracy substantially more (8%) than did adding TSP to sleep disturbance (3%), due to the higher level of overlapping variance between the latter 2. Moreover, addition of TNF- $\alpha$  moved model performance into the good prediction range. Similar examination of predictors of CRPS diagnosis at 6 months indicated nearly 6% shared variance between the widespread pain and pain intensity predictors identified, and

as a result, a combined model produced only 1% better accuracy than pain intensity alone. If a replicated predictive model with good accuracy were developed, it could have clinical utility for identifying patients preoperatively at greater risk for developing CRPS. These individuals then could be monitored more closely for early signs of CRPS and possibly early intervention. For example, patients with emerging CRPS might benefit from corticosteroids, which some work suggests may be effective for CRPS in its early stages.<sup>49,61</sup>

Potential study limitations are noted. First, CRPS in the TKA population may be qualitatively different than CRPS in other settings. Although our CRPS subgroup at 6 months reflected individuals meeting standardized IASP diagnostic criteria, the relatively low pain intensity (median = 3/10) compared to the intense pain often noted by CRPS patients in the pain management setting was notable. The CSS value in those meeting CRPS criteria (median CSS = 6) was also found to be slightly lower than observed in pain management patients recently diagnosed with CRPS (CSS = 8.7).<sup>35</sup> It is not inconceivable that apparent CRPS even 6 months following surgery might yet reflect delayed healing that will resolve without specific intervention. Whether the current results will generalize to predicting CRPS in other settings, such as fracture and traumatic injuries, remains to be demonstrated. Second, the sample consisted largely of non-Hispanic, white, older adults, nearly two-thirds of whom were female. Generalization to different demographic groups (younger, male, more diverse race/ethnicity) should be confirmed in subsequent work. Finally, the study was powered for testing perioperative oxidative stress effects on continuous long-term pain outcomes in the primary project and therefore may not have had sufficient power to detect all relevant CRPS predictive relationships.

In summary, more widespread and intense preoperative pain, and greater pain interference, TSP, and circulating TNF- $\alpha$  were prospectively associated with a greater number of CRPS diagnostic features 6 months post-TKA. Negative affect-related predictors identified at 6-week follow-up did not predict 6-month CRPS outcomes. Whether or not participants met CRPS criteria at 6 months was predicted by more intense and widespread pain preoperatively. The overall pattern of findings supports a role for central sensitization and inflammatory mechanisms in determining postoperative CRPS risk.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2022.04.005>.

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