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RESEARCH ARTICLE

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# Levels of preoperative cerebrospinal fluid pro-inflammatory mediators and chronic pain after total knee arthroplasty surgery

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## Abstract

**Background:** Patients undergoing total knee arthroplasty (TKA) surgery are at high risk of chronic postsurgical pain (CPSP). Accumulating evidence suggests an active role of neuroinflammation in chronic pain. However, its role in the progression to CPSP following TKA surgery remains unanswered. Here, we examined the associations between preoperative neuroinflammatory states and pre- and postsurgical chronic pain in TKA surgery.

**Methods:** The data of 42 patients undergoing elective TKA surgery for chronic knee arthralgia at our hospital were analyzed in this prospective study. Patients completed the following questionnaires: brief pain inventory (BPI), hospital anxiety and depression scale, painDETECT, and pain catastrophizing scale (PCS). Cerebrospinal fluid (CSF) samples were collected preoperatively and concentrations of IL-6, IL-8, TNF, fractalkine, and CSF-1 were measured by electrochemiluminescence multiplex immunoassay. CPSP severity was ascertained, using the BPI, 6 months postsurgery.

**Results:** While no significant correlation was observed between the preoperative CSF mediator levels and preoperative pain profiles, the preoperative fractalkine level in the CSF showed a significant correlation with CPSP severity (Spearman's rho $= -0.525$; $p = .002$). Furthermore, multivariate linear regression analysis revealed that the preoperative PCS score (standardized $\beta$ coefficient [$\beta$]: .11; 95% confidence interval [CI]: 0.06–0.16; $p < .001$) and CSF fractalkine level ($\beta$: $-.62$; 95% CI: $-1.10$ to $-0.15$; $p = .012$) were independent predictors of CPSP severity 6 months after TKA surgery.

Jungo Kato and Reiko Murase contributed equally to this study.

**Conclusions:** We identified the CSF fractalkine level as a potential predictor for CPSP severity following TKA surgery. In addition, our study provided novel insights into the potential role of neuroinflammatory mediators in the pathogenesis of CPSP.

**KEYWORDS**
cerebrospinal fluid, chronic postsurgical pain, fractalkine, neuroinflammation, total knee arthroplasty

**Editorial Comment**

Persistent pain can be an undesirable result after total knee arthroplasty and the mechanism for development of this are not completely understood. In this explorative study, cerebrospinal fluid fractalkine level was found to be associated with severity of chronic postsurgical pain in this cohort. Further study of postoperative neuroinflammation and persistent pain mechanisms is warranted.

## 1 | INTRODUCTION

Despite significant improvements in perioperative pain management, chronic postsurgical pain (CPSP), which persists even after the surgical wound has healed, remains a huge medico-social problem.[1] Although numerous risk factors, such as younger age, female sex, genetic factors, psycho-emotional factors, and preoperative chronic pain, have been reported,[2] the lack of understanding of the mechanisms underlying progression to CPSP has precluded the implementation of effective preventive and therapeutic measures.

Total knee arthroplasty (TKA), a joint replacement surgery for knee joint destruction due to osteoarthritis (OA), rheumatoid arthritis (RA), or trauma, has been recognized as a high-risk procedure for CPSP, with a reported incidence of 13%–44%.[2] Although the mechanisms by which preoperative pain leads to CPSP are unclear, preoperative chronic knee arthralgia is a possible risk factor.[3]

Neuroinflammation is a local inflammation of tissues within the peripheral and central nervous systems (CNS), which is characterized by the activation of immune cells and increased production of inflammatory mediators at these sites.[4] Accumulating evidence suggests a pivotal role of CNS neuroinflammation in the development and maintenance of chronic pain.[5,6] Notably, the microglia, which are bone marrow-derived immune cells in the CNS, may be key players in neuroinflammation via the release of pro-inflammatory mediators in response to peripheral tissue injury.[7,8] These centrally released mediators purportedly induce central sensitization, leading to the augmentation and prolongation of pain.[9–11] Such preoperatively established neuroinflammation in painful knee diseases may contribute to the progression of CPSP.

Moreover, emerging evidence suggests that preoperative pain-related psycho-emotional distress, such as anxiety, pain catastrophizing, and sleep disturbances, may contribute to the transition to CPSP.[2,12] However, little is known about the association between neuroinflammation and a maladaptive psycho-emotional status.

In this prospective cohort study with patients undergoing TKA surgery, we first examined the correlations between preoperative multidimensional pain-related parameters and pro-inflammatory mediator levels in cerebrospinal fluid (CSF) collected immediately before surgery. Second, we analyzed the associations between preoperative multidimensional pain-related parameters, CSF pro-inflammatory mediator levels, and CPSP intensity 6 months postsurgery to explore the involvement of preoperative neuroinflammation in the transition to CPSP. Finally, we sought to establish a prediction model for the intensity of CPSP using perioperative variables, including preoperative CSF pro-inflammatory mediator levels.

## 2 | METHODS

### 2.1 | Study setting and participants

This prospective cohort study was conducted with patients who underwent TKA between September 2017 and October 2019 at Keio University Hospital, Tokyo, Japan. The inclusion criteria were: age of 40–80 years, OA or RA as the primary reason for elective TKA surgery, and chronic knee arthralgia (average numerical rating score >4/10) with a pain duration >3 months. In addition, patients were excluded if they had any of the following conditions: contraindications for spinal anesthesia, severe cognitive or mental disorders, active CNS disease, or pregnancy.

### 2.2 | Data collection

Data on baseline demographics, comorbidities, preoperative pain-related parameters, and surgical and anesthetic parameters were prospectively collected from electronic medical records.

### 2.3 | Multidimensional preoperative pain assessment

All the patients were asked to complete questionnaires, after admission to the hospital, before TKA. All the questionnaires were validated

in Japanese versions. Preoperative pain severity and interference associated with knee arthralgia were measured using the brief pain inventory (BPI), which includes 11-point numeric rating scales.[13] Pain intensity was calculated as the mean of the four items that assessed pain at its worst, its least, on average, and currently, while pain interference was the mean of the items that evaluated pain interference related to seven domains of life (i.e., general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Preoperative anxiety and depression were assessed using the hospital anxiety and depression scale (HADS), a 14-item questionnaire with scores ranging from 0 to 3.[14,15] Half of the questions assessed anxiety, and the rest assessed depression. Each subscale score ranges from 0 to 21. For each item, a score of ≥11 indicates a clinically significant disorder, whereas a score of 8–10 suggests a mild disorder.[15]

The involvement of neuropathic pain-like components in knee arthralgia was evaluated using the painDETECT questionnaire, which consists of nine items with possible scores ranging from 0 to 38 and evaluates pain quality, pattern, and radiation.[16] PainDETECT scores ≧19 indicate the presence of neuropathic pain-like symptoms.[17] Preoperative pain catastrophizing thoughts were quantified using the pain catastrophizing scale (PCS), which reflects the frequency of 13 types of pain-related catastrophizing thoughts or feelings in patients (each scored from 0 to 4). The total PCS scores range from 0 to 52, with a cut-off value ≧30 indicating clinical significance.[18,19]

## 2.4 | Collection of CSF and serum samples

CSF samples (1.5 mL) were collected in polypropylene tubes approximately between 1 and 4 PM during spinal anesthesia for TKA surgery prior to administration of the local anesthetic. The samples were immediately centrifuged at 3000 rpm for 10 min at 4°C to remove cells and debris, and the supernatants were aliquoted, transferred to our laboratory, and stored at −80°C until analyzed. Venous blood samples (10 mL) were collected in a tube containing a coagulant (Venoject II autosep, Termo, Tokyo, Japan) after induction of general anesthesia for TKA surgery. Serum was separated from the samples by centrifugation at 3000 rpm for 10 min at 4°C and stored at −80°C until analyzed. The concentrations of pro-inflammatory cytokines/chemokines, including interleukin (IL)-6, IL-8, tumor necrosis factor (TNF), fractalkine, and colony-stimulating factor (CSF)-1 were analyzed by electrochemiluminescence multiplex immunoassay (Meso Scale Discovery, Rockville, MD). The choice of biomarkers was determined based on the previous studies showing their potential involvement in the pathogenesis of chronic pain and our preliminary data regarding detectability. The assay was performed by the Research Center for Immunological Analysis, Inc. (Okayama, Japan).

## 2.5 | Anesthesia and TKA surgery

All patients received spinal anesthesia with 0.5% bupivacaine, and general anesthesia with sevoflurane or desflurane. Fentanyl and/or remifentanil were administered intraoperatively at the discretion of the attending anesthesiologist. Before the closure of the operated joint, a cocktail containing 187.5 mg of levobupivacaine, 10 mg of morphine, 40 mg of methylprednisolone, and 0.3 mg of adrenalin was injected particularly for acute postoperative pain control. For postsurgical pain control, all patients received intravenous patient-controlled analgesia (iv-PCA) with fentanyl (basal infusion, 10 μg/h; bolus, 20 μg; lockout interval, 10 min) for up to 72 h postsurgery. Moreover, adjunct analgesics, such as nonsteroidal anti-inflammatory drugs, acetaminophen, and tramadol, were provided as needed. TKA surgeries were performed by three experienced surgeons using a standardized medial parapatellar approach with a cement-fixed bearing implant. All patients underwent standardized postoperative physiotherapy and rehabilitation protocols, which allowed continuous passive motions on the operated knee, transfer training, and walking short distance on the first postoperative day. The general goal of the postoperative clinical pathway for TKA was to prepare for patients to discharge from hospital 2–3 weeks after surgery. Patients were allowed to discharge from hospital when they became able to walk with a cane, independently with all transfers.

## 2.6 | Acute postoperative pain assessment

Patients were asked to rate their pain intensity at rest on the visual analog scale (VAS, ranging from 0 = no pain to 100 = worst pain imaginable) 6, 12, 24, 36, 48, 60, and 72 h postsurgery. In addition, the cumulative amount of fentanyl used postoperatively via iv-PCA and the number of PCA bolus requests by postoperative Day 3 were also recorded.

## 2.7 | CPSP assessment

The chronic pain after surgery was characterized by the questionnaires sent to the patients 6 months postsurgery. Based on the answers to the questionnaires and information from the medical records, the diagnosis of CPSP was ascertained by the following criteria, as defined by the IASP classification for ICD-11: postsurgical pain developed or increased in intensity, which had persisted more than 3 months after surgery; pain localized to the surgical field, projected to the innervation territory of a nerve situated in the area or referred to a dermatome; other causes of pain (e.g., infections, malignancy, etc.) were excluded.[20] The intensity of CPSP was quantified in the same manner as BPI pain intensity, as previously described. A BPI pain intensity less than or equal to the median value (= 1.25) was defined as no-to-mild CPSP, while the others were defined as moderate-to-severe CPSP.

## 2.8 | Statistical analyses

In descriptive statistical analyses, categorical data were presented as numbers and percentages, and continuous data as medians and

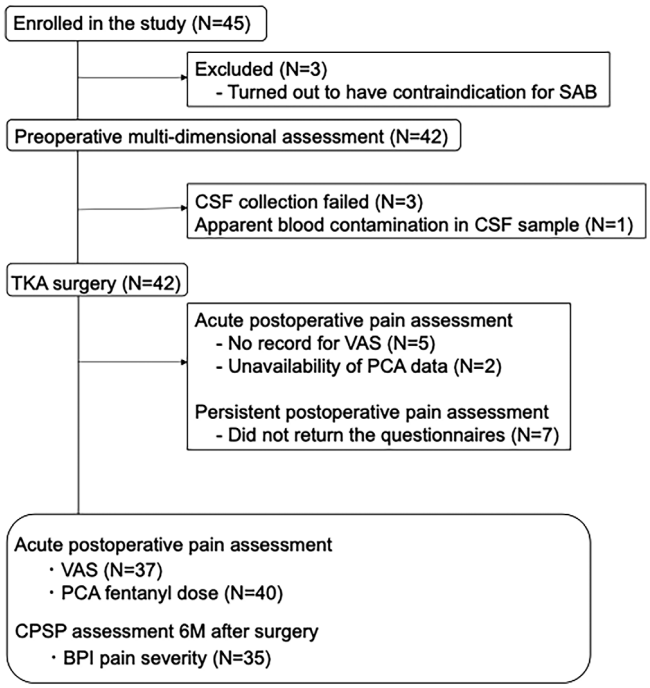


**FIGURE 1** Study flow chart of patient enrollment, follow-up, and sample collection. BPI, brief pain inventory; CPSP, chronic postsurgical pain; CSF, cerebrospinal fluid; M, months; PCA, patient-controlled analgesia; SAB, subarachnoid block; TKA, total knee arthroplasty; VAS, visual analog scale.

interquartile ranges (IQR). The associations between variables were assessed using Spearman's correlation coefficient (rho) using the correlation matrix function in Prism 9 (GraphPad Software, Inc., La Jolla, CA). The number of patients recruited was determined based on the estimation of the minimal sample size for a Spearman's correlation between preoperative and postoperative parameters. The power analysis using IBM SPSS Statistics 27 (IBM Corp., Armonk, NY) with an alpha of 0.05 and a power of 0.80, and a large effect size (rho = 0.5) for a two-tailed test determined the minimal sample size of 35. Having considered the possibilities of unsuccessful CSF sample collection and losses to follow-up, we enrolled 45 patients for the current study. For comparisons between groups, the Mann–Whitney *U* test was used for continuous variables and Fisher's exact test for categorical variables. Univariate linear regression analyses were performed for all putative variables in relation to pain intensity. For exploratory purposes, the variables with $p < .2$ were retained for multivariate linear regression analyses. A multiple linear regression model for the prediction of pain intensity 6 months postsurgery was constructed through the stepwise selection of candidate predictors (entry: $p < .05$; removal: $p > .1$). The adjusted $R^2$ value was calculated to assess model fit. All reported *p* values were two-sided, and values <.05 were considered significant. The Bonferroni correction was applied to multiple tests. Missing data points were excluded from the pairwise comparison and correlation analyses. Data analyses were performed using IBM SPSS Statistics 27 and Prism 9.

**TABLE 1** Baseline characteristics of the patients and the procedural data.

| Variable | Median (IQR) or *N* |
|---|---|
| Demographic | |
| Age, y.o., median (IQR) | 70.5 (65.75–75.25) |
| Sex, F/M | 33/9 |
| BMI, Kg $m^{-2}$, median (IQR) | 26.5 (23.75–29.0) |
| Medical history | |
| HTN, *N* (%) | 23 (54.8) |
| DM, *N* (%) | 6 (14.2) |
| Medications | |
| NSAIDS, *N* (%) | 14 (33.3) |
| Opioid analogs, *N* (%) | 7 (16.7) |
| Gabapentinoids, *N* (%) | 3 (7.1) |
| Anti-psychotics, *N* (%) | 9 (21.4) |
| Immunosuppressants, *N* (%) | 9 (21.4) |
| Pain-related | |
| Dx. OA/RA/others | 36/5/1 |
| Duration of joint pain, months, median (IQR) | 60.0 (36.0–120.0) |
| Previous knee surgery, no/ipsi./contra./bilateral | 25/3/12/2 |
| Procedural | |
| Unilateral/bilateral surgery | 35/7 |
| Anesthesia time, min, median (IQR) | 178.5 (160.5–215.25) |
| Operation time, min, median (IQR) | 117.0 (109.0–149.5) |
| Fentanyl, mg, median (IQR) | 0.100 (0.100–0.200) |
| Remifentanil, mg, median (IQR) | 0.442 (0–0.779) |

Abbreviations: BMI, body mass index; DM, diabetes mellitus; Dx, diagnosis; F, female; HTN, hypertension; IQR, interquartile range; M, male; NSAIDS, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; RA, rheumatoid arthritis.

## 3 | RESULTS

### 3.1 | Baseline characterization of the participants

Patient enrolment in this study and data availability for each assessment are shown in Figure 1. Of the 42 patients, CSF samples from 38 patients were available for further analysis. Thirty-five patients responded to the questionnaires 6 months after TKA surgery. Baseline demographic and procedural data are summarized in Table 1. Most of the participants had OA-derived chronic knee arthralgia, and 40.4% (17 of 42 participants) had undergone prior knee surgery on the ipsilateral or contralateral side. Cumulatively, 16.7% (seven of the 42 participants) underwent bilateral TKA during surgery. All surgeries were completed successfully. No adverse events associated with anesthesia or surgery were reported.

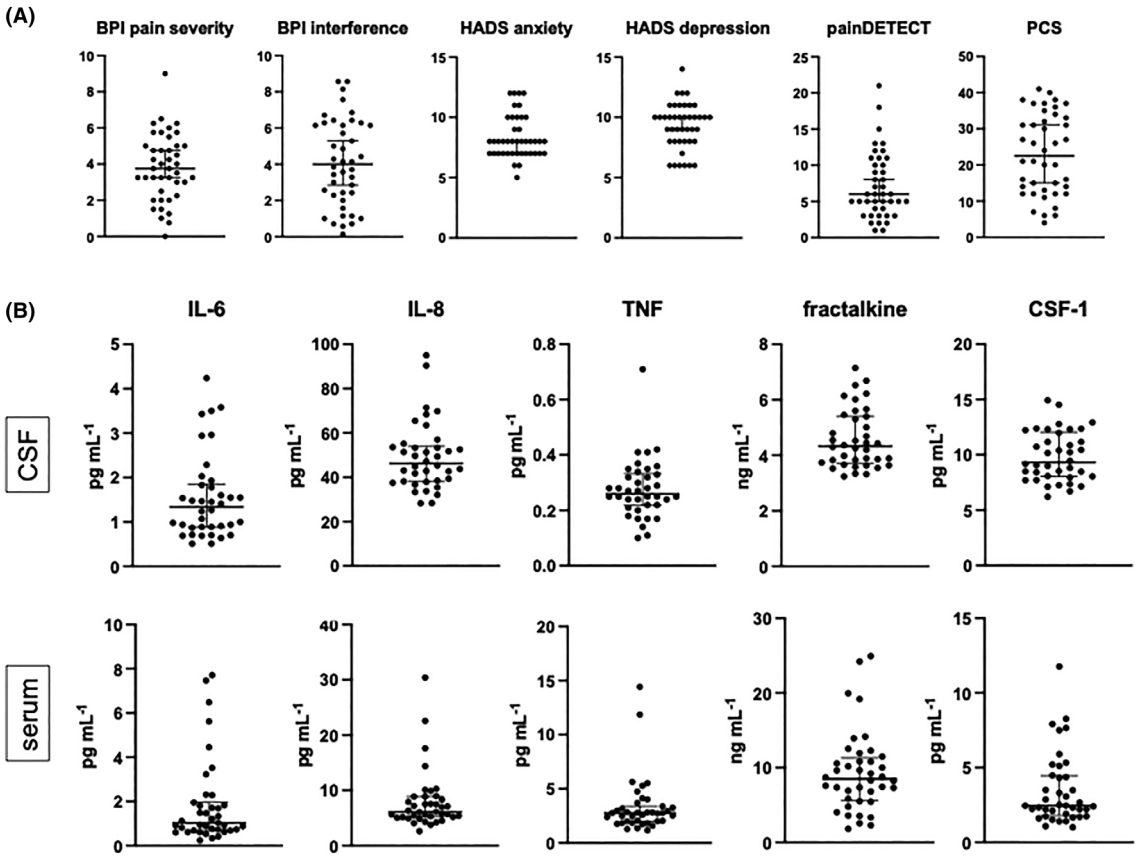


**FIGURE 2** Distributions of the scores in preoperative multidimensional pain assessments (A) and levels of pro-inflammatory mediators in the cerebrospinal fluid and serum collected immediately before surgery (B). The horizontal bars represent the median and the interquartile range. BPI, brief pain inventory; CSF, cerebrospinal fluid; CSF-1, colony stimulating factor-1; HADS, hospital anxiety and depression scale; IL, interleukin; PCS, pain catastrophizing scale; TNF, tumor necrosis factor.

## 3.2 | Associations between CSF/serum analytes and preoperative parameters

The score distributions in the preoperative multidimensional pain assessments and the concentrations of the neuroinflammation markers in the CSF and serum samples are shown in Figure 2. Correlation analyses between the CSF analytes (Figure 3A, Table S1) revealed strong correlations between IL-6 and IL-8 (Spearman's rho = 0.561, $p < .001$) and between fractalkine and CSF-1 (rho = 0.728, $p < .001$), and modest correlations between IL-8 and fractalkine (rho = 0.346, $p = .033$) and between IL-8 and CSF-1 (rho = 0.342, $p = .036$). After Bonferroni adjustment (0.05/10 = 0.005), the correlations between IL-6 and IL-8 and between fractalkine and CSF-1 remained significant. However, no significant correlation was observed between the CSF and serum concentrations of either analyte (Figure 3B, Table S2). The correlations between the concentrations of CSF analytes and the preoperative demographic and pain-related data are shown in Figure 3C and Table S3. A weak negative correlation was observed between the painDETECT score and fractalkine (rho = −0.419, $p = .009$). However, after the Bonferroni adjustment (0.05/45 = 0.0011), the correlation became insignificant. A subgroup analysis comparing the levels of CSF analytes between patients with and without NSAIDs use showed no statistically significant differences, except in the IL-8 level (no NSAIDs: median 49.6 pg $mL^{-1}$, IQR 41.2 to 63.9 pg $mL^{-1}$; versus NSAIDs: median 40.9 pg $mL^{-1}$, IQR 33.0 to 51.6 pg $mL^{-1}$, $p = .045$; Table S4).

## 3.3 | Association of perioperative parameters and persistent postoperative pain 6 months after TKA surgery

The correlations between the preoperative demographics, pain-related data, levels of CSF analytes, and the severity of CPSP 6 months after surgery are shown in Figure 4 and Table S5. Among those variables, painDETECT (rho = 0.614, $p < .001$), PCS (rho = 0.665, $p < .001$), fractalkine (rho = −0.525, $p = .002$), and CSF-1 (rho = −0.442, $p = .013$) showed significant correlations; painDETECT, PCS, and fractalkine remained significant after Bonferroni adjustment (0.05/14 = 0.0036). The characteristics of patients, including demographic variables, preoperative pain-related multidimensional profiles, preoperative CSF/serum variables, procedural variables, and acute postoperative pain, stratified according to the severity of CPSP 6 months after TKA surgery, are

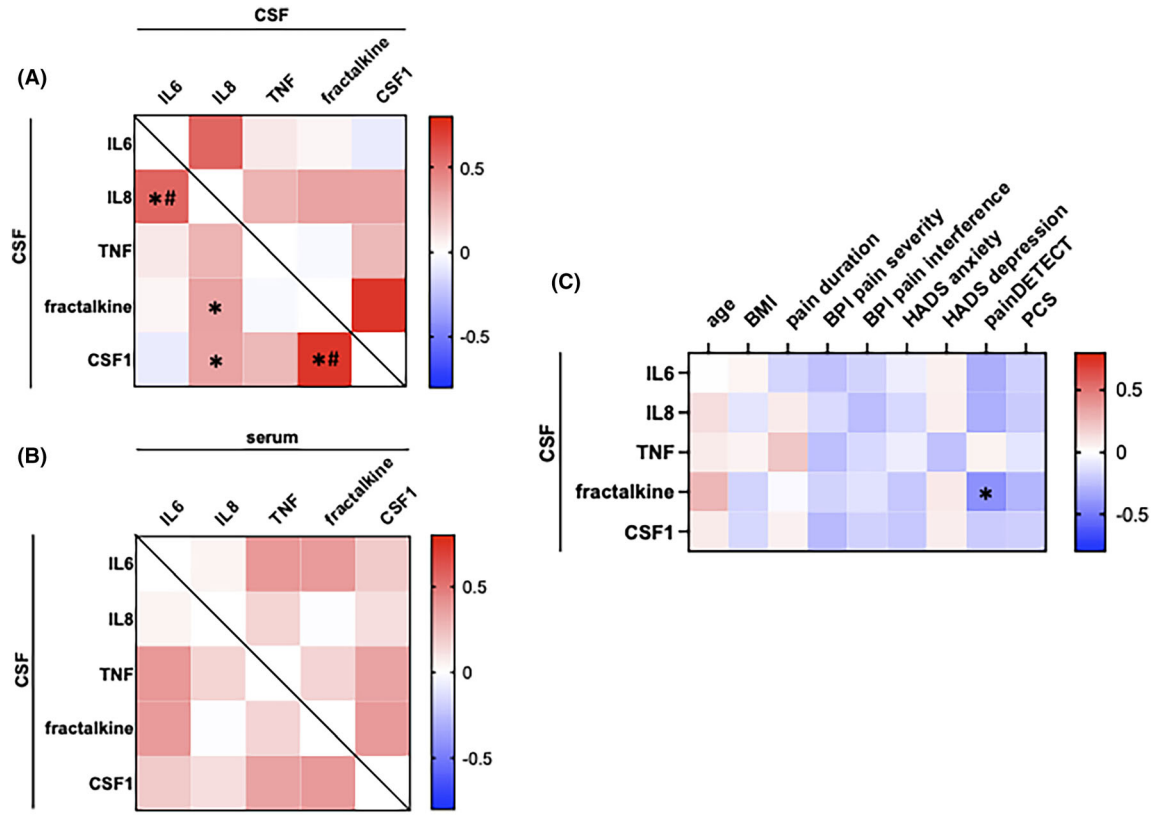


**FIGURE 3** Heat map demonstration of Spearman correlation coefficient (rho) between cerebrospinal fluid neuroinflammatory markers (A), between cerebrospinal fluid and serum markers (B), and between cerebrospinal fluid markers and demographic and preoperative pain-related parameters (C). Red and blue colors illustrate positive and negative correlations, respectively. *$p < .05$, uncorrected for multiple testing. # denotes the correlation that remained significant after Bonferroni adjustment. BMI, body mass index; BPI, brief pain inventory; CSF, cerebrospinal fluid; CSF-1, colony stimulating factor-1; HADS, hospital anxiety and depression scale; IL, interleukin; PCS, pain catastrophizing scale; TNF, tumor necrosis factor.

shown in Table 2. Patients with moderate-to-severe CPSP had significantly higher scores for preoperative BPI pain severity (median 4.0, IQR: 3.3–5.0; versus no-to-mild CPSP: median 2.9, IQR: 1.6–4.1; $p = .034$), HADS anxiety (median 8.0, IQR: 7.0–10.0; versus no-to-mild CPSP: median 7.0, IQR: 7.0–8.0; $p = .044$), painDETECT (median 9.0, IQR: 6.0–12.0; versus no-to-mild CPSP: median 3.5, IQR: 2.0–6.5; $p < .001$), and PCS (median 30.0, IQR: 21.0–37.0; versus no-to-mild CPSP: median 12.0, IQR: 7.3–19.0; $p < .001$) compared to patients with no-to-mild CPSP. A subgroup analysis revealed no significant group difference in the degree of preoperative sleep disturbances evaluated in the sleep interference item of the BPI (no-to-mild CPSP: median 2.0, IQR 0.0–4.0; moderate-to-severe CPSP: median 4.0, IQR 1.0–7.0; $p = .193$). Furthermore, the participants with moderate-to-severe CPSP had significantly lower levels of fractalkine (median 3.84 ng $mL^{-1}$, IQR: 3.59–4.40 ng $mL^{-1}$; versus no-to-mild CPSP: median 5.15 ng $mL^{-1}$, IQR: 4.14–6.24 ng $mL^{-1}$; $p < .001$) and CSF-1 (median 8.51 pg $mL^{-1}$, IQR: 7.48–9.79 pg $mL^{-1}$; versus no-to-mild CPSP: median 10.9 pg $mL^{-1}$, IQR: 9.23–12.3 pg $mL^{-1}$; $p = .008$) in the preoperative CSF than patients with no-to-mild CPSP. After Bonferroni adjustment ($0.05/33 = 0.0015$), the differences between the groups in the painDETECT and PCS scores, and fractalkine levels, remained significant. However, no significant differences were observed in other parameters between the participants with no-to-mild and moderate-to-severe CPSP 6 months postsurgery.

### 3.4 | Predictors of CPSP severity and pain interference in multivariate linear regression models

Univariate linear regression analyses revealed that preoperative BPI pain severity (standardized $\beta$ coefficient [$\beta$]:.38; 95% confidence interval [CI]: 0.001–0.760; $p = .049$), BPI pain interference ($\beta$: .33; 95% CI: 0.05–0.62; $p = .024$), HADS anxiety ($\beta$: .52; 95% CI: 0.13–0.91; $p = .011$), painDETECT ($\beta$:.29; 95% CI: 0.17–0.41; $p < .001$), PCS ($\beta$: .13; 95% CI: 0.08–0.17; $p < .001$), CSF fractalkine ($\beta$: −.87; 95% CI: −1.55 to −0.18; $p = .015$), and CSF CSF-1 ($\beta$: −.38; 95% CI: −0.73 to −0.04; $p = .030$) were significantly associated with the severity of CPSP 6 months after TKA (Table 3). In multivariate linear regression analyses, the preoperative PCS scores ($\beta$: .11; 95% CI: 0.06–0.16; $p < .01$) and CSF fractalkine levels ($\beta$: −.62; 95% CI: −1.10 to −0.15; $p = .012$) were significant predictors of the severity of CPSP 6 months after TKA (Table 4).

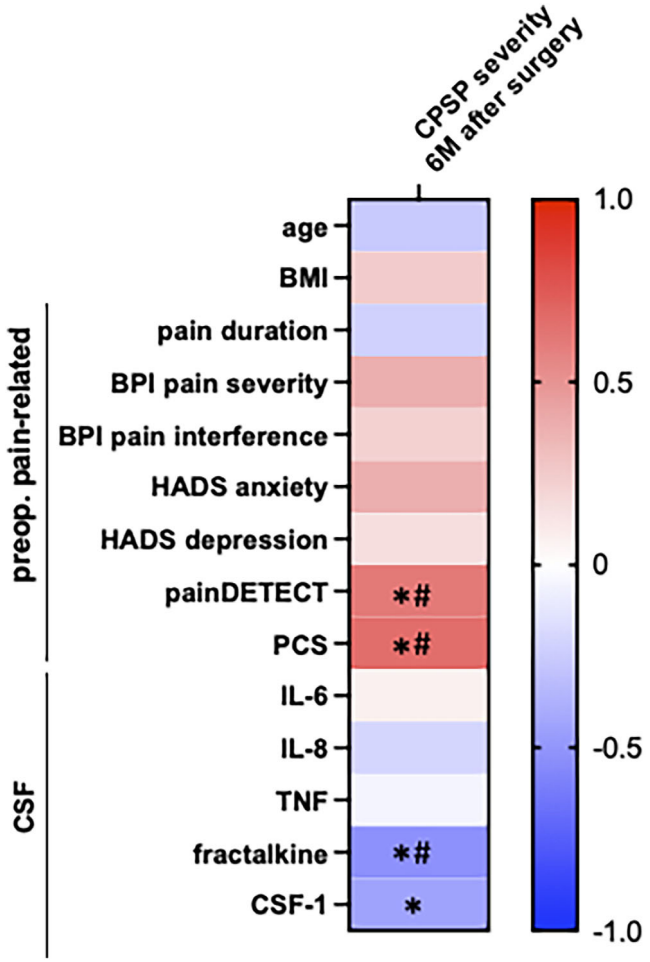


**FIGURE 4** Heat map demonstration of Spearman correlation coefficient (rho) between preoperative demographic, pain-related parameters and cerebrospinal fluid neuroinflammatory markers, and pain severity 6 months after surgery. Red and blue colors illustrate positive and negative correlations, respectively. *$p < .05$, uncorrected for multiple testing. # denotes correlation that remained significant after Bonferroni adjustment. BMI, body mass index; BPI, brief pain inventory; CSF, cerebrospinal fluid; CSF-1, colony stimulating factor-1; HADS, hospital anxiety and depression scale; IL, interleukin; M, month; PCS, pain catastrophizing scale; TNF, tumor necrosis factor.

## 4 | DISCUSSION

In this study, the preoperative CSF fractalkine level and the PCS score were independent predictors of CPSP intensity 6 months after TKA surgery. To the best of our knowledge, this is the first study to longitudinally examine the associations between the levels of preoperative inflammatory mediators in the CSF and preoperative and postoperative chronic pain profiles in knee arthralgia patients undergoing TKA surgery.

Several significant positive correlations between the pro-inflammatory mediators in the preoperative CSF were observed in TKA patients in this study. Conversely, the lack of clear correlations between the levels of these pro-inflammatory mediators in the CSF and multidimensional preoperative pain scores contradict our initial hypothesis, and the results of previous studies suggesting a causative role of neuroinflammation in the maintenance phase of chronic pain.[5]

One explanation for this discrepancy is the difference in the underlying pathophysiology of pain. The pain experienced by the participants might have resulted mainly from a peripheral sensitization mechanism induced by the progression of joint destruction, where CNS neuroinflammation plays a minor role in the severity of the pain.[21] However, in other instances, OA/RA patients have disproportionately severe joint pain with mild joint destruction, where the central sensitization mechanisms are more likely to be the major cause of chronic pain.[21–23] In those circumstances, painful injuries, such as local inflammation and nerve injury, cause hyperactivity of nociceptors accompanied by the activation of glial cells in the CNS, resulting in neuroinflammation.[24] Such neuroinflammatory processes are considered to contribute to the maintenance of central sensitization via the actions of released pro-inflammatory mediators and neuromodulators, leading to the persistence of pain, even after the resolution of peripheral causes.[24] Consistently, IL-8 concentrations in the CSF have proven to positively correlate with increased pain and hyperalgesia in lumber disk herniation patients.[25] Moreover, the CSF levels of pro-inflammatory mediators, including Fms-related tyrosine kinase 1 and interferon gamma-induced protein (IP)-10, have been reported to be associated with signs of central sensitization in hip OA patients.[26] Therefore, the characterization of inflammatory profiles in the CSF may be of clinical value to delineate which peripheral or central mechanisms play a major role in knee arthralgia and ascertain which patients may benefit from surgical intervention.

Furthermore, although neuroinflammation is generally thought to be deleterious, emerging evidence suggests a more complex role of neuroinflammation in pathological processes in the CNS. Recent brain PET imaging studies demonstrated elevated levels of translocator protein (TSPO), a marker of glial activation, in multiple brain regions in fibromyalgia[27] and chronic low back pain patients.[28] Interestingly, the thalamic levels of TSPO were rather shown to be negatively correlated with clinical pain and circulating levels of IL-6.[28] Several lines of evidence from animal studies have also challenged the detrimental role of neuroinflammation in the maintenance phase of chronic pain. While intrathecal anti-TNF treatment prevented mechanical and thermal hypersensitivity in rodent neuropathic pain models, delayed anti-TNF treatment failed to reverse already-established hypersensitivity,[29,30] implying that TNF's role in the maintenance of neuropathic pain may be of marginal importance. Additionally, intrathecal IL-6 inhibited C-fiber activity and neuronal hyperexcitability in neuropathic rats, indicating a potential anti-nociceptive role of spinal IL-6.[31] Indeed, several clinical observational studies have also failed to demonstrate a positive correlation between neuroinflammation and pain severity in patients with OA.[32–34]

Conversely, in this study, the data showed that elevated preoperative CSF fractalkine levels were independently associated with less intense CPSP 6 months postsurgery. CSF-1 exhibited a similar trend of negative correlation with CPSP, although the correlation became insignificant after adjustment for multiple comparisons. These negative correlations were unexpected, given the pro-nociceptive effects

**TABLE 2** Comparison of preoperative, procedural, and acute postoperative variables stratified according to the severity of chronic postoperative pain at 6 months after TKA surgery.

| | No-mild pain ($N = 16$) | Moderate-severe pain ($N = 19$) | *p*-value |
|---|---|---|---|
| Demographic | | | |
| Age, y.o. median (IQR) | 71.5 (69.0–76.0) | 68.0 (68.0–76.0) | .142 |
| Sex, F/M | 14/2 | 12/7 | .104 |
| BMI, Kg $m^{-2}$, median (IQR) | 26.0 (23.0–28.8) | 28.0 (24.0–30.0) | .385 |
| Systemic complications | | | |
| HTN, *N* (%) | 10 (62.5) | 8 (42.1) | .194 |
| DM, *N* (%) | 4 (25.0) | 1 (5.3) | .120 |
| Medication | | | |
| NSAIDS, *N* (%) | 4 (25.0) | 8 (42.1) | .242 |
| Opioid analogs, *N* (%) | 3 (18.8) | 4 (21.1) | .602 |
| Gabapentinoids, *N* (%) | 0 (0.0) | 3 (15.8) | .148 |
| Anti-psychotics, *N* (%) | 1 (6.3) | 6 (31.6) | .072 |
| Immunosuppressants, *N* (%) | 3 (18.8) | 5 (26.3) | .452 |
| Preop. pain-related variables | | | |
| Dx. OA/RA/others | 13/2/1 | 16/3/0 | .415 |
| Duration of joint pain, months, median (IQR) | 72.0 (18.0–165.0) | 55.0 (36.0–71.0) | .204 |
| Previous knee surgery, no/ipsi./contra./bilateral | 10/0/5/1 | 10/3/5/1 | .532 |
| BPI pain severity, median (IQR) | 2.9 (1.6–4.1) | 4.0 (3.3–5.0) | .034* |
| BPI pain interference, median (IQR) | 3.1 (1.8–4.8) | 4.4 (2.0–6.3) | .350 |
| HADS anxiety, median (IQR) | 7.0 (7.0–8.0) | 8.0 (7.0–10.0) | .044* |
| HADS depression, median (IQR) | 9.5(8.0–10.8) | 10.0 (8.0–11.0) | .683 |
| PainDETECT, median (IQR) | 3.5 (2.0–6.5) | 9.0 (6.0–12.0) | <.001*,[a] |
| PCS, median (IQR) | 12.0 (7.3–19.0) | 30.0 (21.0–37.0) | <.001*,[a] |
| Preop. CSF analytes | | | |
| IL-6, pg $mL^{-1}$, median (IQR) | 1.36 (0.84–2.95) | 1.47 (0.90–1.80) | .953 |
| IL-8, pg $mL^{-1}$, median (IQR) | 52.0 (41.0–58.6) | 47.2 (37.1–52.3) | .200 |
| TNF, pg $mL^{-1}$, median (IQR) | 0.26 (0.17–0.33) | 0.25 (0.22–0.32) | .799 |
| Fractalkine, ng $mL^{-1}$, median (IQR) | 5.15 (4.14–6.24) | 3.84 (3.59–4.40) | <.001*,[a] |
| CSF-1, pg $mL^{-1}$, median (IQR) | 10.9 (9.23–12.3) | 8.51 (7.48–9.79) | .008* |
| Procedural | | | |
| Unilateral/bilateral surgery | 15/1 | 14/5 | .131 |
| Anesthesia time, min, median (IQR) | 177.5 (162.8–186.8) | 179.0 (159.0–247.0) | .561 |
| Operation time, min, median (IQR) | 116.5 (109.5–130.5) | 131.0 (109.0–185.0) | .271 |
| Fentanyl, mg, median (IQR) | 0.100 (0.100–0.200) | 0.100 (0.100–0.200) | .635 |
| Remifentanil, mg, median (IQR) | 0.442 (0.270–0.711) | 0.400 (0–0.915) | .612 |
| Acute postop. Variables | | | |
| PCA request, *N*, median (IQR) | 9.0 (5.0–19.0) | 19.0 (8.0–36.5) | .215 |
| Total postoperative fentanyl, mg, median (IQR) | 0.68 (0.57–0.90) | 0.81 (0.65–1.01) | .274 |
| Postoperative VAS average, median (IQR) | 24.0 (19.9–36.1) | 38.9 (21.9–48.4) | .125 |
| Postoperative VAS max, median (IQR) | 50. 0(35.0–76.0) | 73.5 (53.8–85.5) | .051 |

Abbreviations: BMI, body mass index; BPI, brief pain inventory; DM, diabetes mellitus; Dx, diagnosis; F, female; HADS, hospital anxiety and depression scale; HTN, hypertension; IQR, interquartile range; M, male; NSAIDS, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PCS, pain catastrophizing scale; VAS, visual analog scale.

[a]Denotes correlation that remained significant after Bonferroni adjustment.

*$p < .05$, uncorrected for multiple comparisons.

of these spinally released mediators on the initiation and maintenance of pathological pain via activation of microglia, reported in rodent models of chronic pain.[35,36] In addition to elucidating chronic pain models, emerging clinical evidence has also revealed the anti-inflammatory effects of fractalkine and CSF-1 in neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.[37–43] These two factors promote microglial polarization toward an M2-like anti-inflammatory phenotype, suppressing the ability to release pro-inflammatory factors in rodent models.[44,45] Recently, Palada et al. reported the protective effects of neuroinflammation in OA patients, which included elevated levels of fractalkine and CSF-1 in the CSF.[32] Considering the pleiotropic effects of these factors, higher preoperative CSF fractalkine and CSF-1 might have produced an anti-inflammatory environment, which could suppress the activation of microglia toward the M1-like pro-inflammatory phenotype triggered by TKA surgery, thereby preventing the development of CPSP. Finally, our data also substantiated the PCS as a relevant independent predictor of the severity of postoperative pain in the chronic phase following TKA surgery. A recent meta-analysis of functional magnetic resonance imaging studies examining the neural substrates of chronic pain demonstrated aberrant connectivities between brain areas tightly associated with anticipation of and attention to pain, and affective and evaluative aspects of pain. These brain areas include the medial frontal cortex, anterior cingulate gyrus, prefrontal cortex, and amygdala.[46] Such aberrant brain connections may also serve as neural substrates that prolong the perception of postoperative pain, leading to chronic pain after successful surgical correction of the original cause of the pain. As the preoperative PCS score showed the highest positive correlation with the intensity of CPSP, such brain mechanisms may play a major role in the pathogenesis of CPSP and may therefore be a target for CPSP prevention. The lack of a positive correlation between the CSF pro-inflammatory mediator levels and the preoperative PCS, HADS anxiety, or HADS depression scores in the current study suggests an active role of central inflammation in the maintenance of preoperative maladaptive psycho-emotional status. Although our data suggest that preoperative neuroinflammation and maladaptive psycho-emotional status may influence the transition to CPSP via different mechanisms, their associations require further scrutiny.

Our study had several limitations. First, because of the small sample size, the effects of other important clinical variables, such as sex, the causes of knee arthralgia, and medication, on the relationships between preoperative neuroinflammation, preoperative pain status, and CPSP could not be fully evaluated. Therefore, the current study should be considered an exploratory rather than a confirmatory study. Second, because the CSF was collected preoperatively only once, it is uncertain

**TABLE 3** Univariate linear regression analysis for chronic postsurgical pain severity at 6 months after TKA surgery.

| | CPSP severity | |
|---|---|---|
| **Variables** | **$\beta$ (95% CI)** | ***p*-value** |
| Demographic | | |
| Age | −.037 (−0.17, 0.10) | .572 |
| BMI | .17 (−0.05, 0.39) | .125 |
| Sex (female) | −1.29 (−2.88, 0.29) | .107 |
| Preoperative pain-related variables | | |
| Pain duration | −.005 (−0.017, 0.008) | .444 |
| BPI pain severity | .38 (0.001, 0.760) | .049* |
| BPI pain interference | .33 (0.05, 0.62) | .024* |
| HADS anxiety | .52 (0.13, 0.91) | .011* |
| HADS depression | .26 (−0.12, 0.64) | .173 |
| PainDETECT | .29 (0.17, 0.41) | <.001* |
| PCS | .13 (0.08, 0.17) | <.001* |
| Preoperative cerebrospinal fluid analytes | | |
| IL-6 | −.19 (−1.03, 0.66) | .658 |
| IL-8 | −.03 (−0.09, 0.03) | .324 |
| TNF | −1.80 (−8.99, 5.39) | .612 |
| Fractalkine | −.87 (−1.55, −0.18) | .015* |
| CSF-1 | −.38 (−0.73, −0.04) | .030* |
| Acute postoperative pain | | |
| PCA request | .01 (−0.03, 0.05) | .579 |
| PCA fentanyl | .81 (−1.56, 3.18) | .491 |
| VAS max. | .02 (−0.01, 0.05) | .182 |
| VAS ave. | −.005 (−0.050, 0.040) | .826 |

Abbreviations: BMI, body mass index; BPI, brief pain inventory; CI, confidence interval; CPSP, chronic postsurgical pain; CSF, colony-stimulating factor; HADS, hospital anxiety and depression scale; IL, interleukin; PCA, patient-controlled analgesia; PCS, pain catastrophizing scale; TKA, total knee arthroplasty; TNF, tumor necrosis factor; VAS, visual analog scale.
*$p < .05$, uncorrected for multiple testings.

**TABLE 4** Variables in the multiple linear regression model for prediction of chronic postsurgical pain severity at 6 months after TKA surgery.

| | Variable | $\beta$-coefficient (95% CI) | *p*-value | $R^2$ |
|---|---|---|---|---|
| CPSP severity 6M after surgery | PCS | .11 (0.06, 0.16) | <.001 | 0.586 (adjusted: 0.552) |
| | CSF fractalkine | −.62 (−1.10, −0.15) | .012 | |

*Note*: The following variables with *p*-values <.2 in the univariate linear regression analysis (Table 3) were entered in this stepwise multiple linear regression analysis: BMI, sex, BPI pain severity, BPI pain interference, HADS anxiety, HADS depression, PainDETECT, PCS, CSF fractalkine, CSF CSF-1, acute postoperative VAS max.
Abbreviations: BMI, body mass index; BPI, brief pain inventory; CI, confidence interval; CPSP, chronic postsurgical pain; CSF, cerebrospinal fluid; HADS, hospital anxiety and depression scale; M, months; PCS, pain catastrophizing scale; PCS, pain catastrophizing scale; TKA, total knee arthroplasty; VAS, visual analog scale.

how the neuroinflammatory status changed before and after surgery; therefore, the mechanism by which the preoperative neuroinflammatory status influenced the development of CPSP remains speculative. Although ethically more challenging, repeated postoperative CSF sampling may provide more mechanistic insights. A recent study showed the CSF levels of most pro-inflammatory mediators, including IL-6 and IL-8, were comparable before and after surgery in hip OA patients. Interestingly, in this longitudinal study, increases in the levels of CSF IP-10 after surgery were found to be associated with increases in pressure pain thresholds.[47] Additional studies with wider repertoire of inflammatory mediators are needed to establish the causative link between neuroinflammation and CPSP. In addition, the levels of pro-inflammatory mediators in the CSF can potentially be affected by preoperative medications. The previous report showed no major effects of NSAIDs use on the levels of pro-inflammatory mediators in the CSF.[48] Our subgroup analysis showed a significant association of NSAIDs use on the level of IL-8 in the CSF, while the use of NSAIDS was not significantly associated with CPSP severity. Further studies are mandatory to characterize the influence of medications with drugs with anti-inflammatory profiles, such as NSAIDs and steroids, on pro-inflammatory mediators in the CSF, as well as the development of CPSP. Third, our anesthetic and analgesic regimen differs from the current recommendations for pain management after TKA surgery, particularly regarding the application of peripheral nerve block and use of opioids.[49] Such differences may potentially have impacted the patients' outcomes including the development of CPSP. The association between the perioperative pain management and transition to CPSP warrants further research. Furthermore, the quantification of pain and psychological/emotional status in this study were mostly derived from self-evaluated patient responses to the questionnaires. The incorporation of other modalities, such as functional MRI studies targeting the aforementioned brain area activities, and quantitative sensory testing, may provide additional objective and quantitative information on the associations between preoperative neuroinflammation, preoperative pain status, and CPSP. Moreover, our study lacked data on pro-inflammatory mediator levels in the CSF of healthy controls. Therefore, it was impossible to determine whether the mediator levels in our study patients were relatively high or low compared to those in the general population. Although a Swedish study reported higher fractalkine levels in the CSF of chronic knee OA patients compared to those in CSF controls from younger headache patients with no signs of inflammation in the CNS,[32] this aspect may be worth investigating in larger scales with optimal healthy control groups.

Cumulatively, our study results corroborate the utility of incorporating preoperative multidimensional pain profiles, including the PCS, in the prediction of CPSP after TKA surgery. While the preoperative profiling of neuroinflammation in the CSF provided limited information for characterizing preoperative pain, the preoperative fractalkine level in the CSF can be a potential marker for predicting postoperative pain intensity in the chronic phase after TKA surgery. Although further studies are warranted, the modulation of neuroinflammation and the deployment of interventions to mitigate aberrant psychological/emotional responses to pain may help prevent the transition to CPSP.

## AUTHOR CONTRIBUTIONS

Jungo Kato, Yasuo Niki, Shizuko Kosugi, and Hiroshi Morisaki conceived and designed the study; Jungo Kato, Reiko Murase, Rie Minoshima, Yasuo Niki, and Shizuko Kosugi collected samples and data; Jungo Kato, Fanglin Lu, Tomoko Toramaru, and Shizuko Kosugi performed data analyses and interpretations; Jungo Kato, Reiko Murase, and Shizuko Kosugi wrote the manuscript. All the authors read and approved the final version of this manuscript. All the authors agreed to be accountable for all aspects of the work.

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## DATA AVAILABILITY STATEMENT

The full-de-identified datasets are available from the corresponding author upon reasonable request.

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## REFERENCES

1. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede R-D. Pain TITftCoC. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain*. 2019;160:45-52.
2. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. *Pain Rep*. 2017;2:e627.
3. Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth*. 2015;114:551-561.
4. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. *Nat Rev Drug Discov*. 2014;13:533-548.
5. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology*. 2018;129:343-366.
6. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth*. 2019;33:131-139.
7. Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR. Microglia in pain: detrimental and protective roles in pathogenesis and resolution of pain. *Neuron*. 2018;100:1292-1311.
8. Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. *Nat Rev Neurosci*. 2018;19:138-152.
9. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci*. 2003;26:696-705.
10. Liu Y, Zhou LJ, Wang J, et al. TNF-α differentially regulates synaptic plasticity in the hippocampus and spinal cord by microglia-dependent mechanisms after peripheral nerve injury. *J Neurosci*. 2017;37:871-881.
11. Nguyen PT, Dorman LC, Pan S, et al. Microglial remodeling of the extracellular matrix promotes synapse plasticity. *Cell*. 2020;182:388-403.e15.
12. Varallo G, Giusti EM, Manna C, et al. Sleep disturbances and sleep disorders as risk factors for chronic postsurgical pain: a systematic review and meta-analysis. *Sleep Med Rev*. 2022;63:101630.
13. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore*. 1994;23:129-138.

14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-370.
15. Duivenvoorden T, Vissers MM, Verhaar JA, et al. Anxiety and depressive symptoms before and after total hip and knee arthroplasty: a prospective multicentre study. *Osteoarthr Cartil*. 2013;21:1834-1840.
16. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911-1920.
17. Larsen DB, Laursen M, Edwards RR, Simonsen O, Arendt-Nielsen L, Petersen KK. The combination of preoperative pain, conditioned pain modulation, and pain catastrophizing predicts postoperative pain 12 months after total knee arthroplasty. *Pain Med*. 2021;22:1583-1590.
18. Sullivan MJLB, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*. 1995;7:524-532.
19. Darnall BD, Sturgeon JA, Cook KF, et al. Development and validation of a daily pain catastrophizing scale. *J Pain*. 2017;18:1139-1149.
20. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain*. 2019;160:45-52.
21. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *Eur J Pain*. 2014;18:1367-1375.
22. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum*. 2013;65:363-372.
23. Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum*. 2012;41:556-567.
24. Ji RR, Chamessian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. *Science*. 2016;354:572-577.
25. Palada V, Ahmed AS, Finn A, Berg S, Svensson CI, Kosek E. Characterization of neuroinflammation and periphery-to-CNS inflammatory cross-talk in patients with disc herniation and degenerative disc disease. *Brain Behav Immun*. 2019;75:60-71.
26. Bjurström MF, Bodelsson M, Montgomery A, et al. Differential expression of cerebrospinal fluid neuroinflammatory mediators depending on osteoarthritis pain phenotype. *Pain*. 2020;161:2142-2154.
27. Albrecht DS, Forsberg A, Sandström A, et al. Brain glial activation in fibromyalgia—a multi-site positron emission tomography investigation. *Brain Behav Immun*. 2019;75:72-83.
28. Loggia ML, Chonde DB, Akeju O, et al. Evidence for brain glial activation in chronic pain patients. *Brain*. 2015;138:604-615.
29. Svensson CI, Schäfers M, Jones TL, Powell H, Sorkin LS. Spinal blockade of TNF blocks spinal nerve ligation-induced increases in spinal P-p38. *Neurosci Lett*. 2005;379:209-213.
30. Marchand F, Tsantoulas C, Singh D, et al. Effects of etanercept and minocycline in a rat model of spinal cord injury. *Eur J Pain*. 2009;13:673-681.
31. Flatters SJL, Fox AJ, Dickenson AH. Spinal interleukin-6 (IL-6) inhibits nociceptive transmission following neuropathy. *Brain Res*. 2003;984:54-62.
32. Palada V, Ahmed AS, Freyhult E, et al. Elevated inflammatory proteins in cerebrospinal fluid from patients with painful knee osteoarthritis are associated with reduced symptom severity. *J Neuroimmunol*. 2020;349:577391.
33. Lundborg C, Hahn-Zoric M, Biber B, Hansson E. Glial cell line-derived neurotrophic factor is increased in cerebrospinal fluid but decreased in blood during long-term pain. *J Neuroimmunol*. 2010;220:108-113.
34. Kosek E, Finn A, Ultenius C, Hugo A, Svensson C, Ahmed AS. Differences in neuroimmune signalling between male and female patients suffering from knee osteoarthritis. *J Neuroimmunol*. 2018;321:49-60.
35. Guan Z, Kuhn JA, Wang X, et al. Injured sensory neuron-derived CSF1 induces microglial proliferation and DAP12-dependent pain. *Nat Neurosci*. 2016;19:94-101.
36. Okubo M, Yamanaka H, Kobayashi K, et al. Macrophage-colony stimulating factor derived from injured primary afferent induces proliferation of spinal microglia and neuropathic pain in rats. *PLoS One*. 2016;11:e0153375.
37. Cardona AE, Pioro EP, Sasse ME, et al. Control of microglial neurotoxicity by the fractalkine receptor. *Nat Neurosci*. 2006;9:917-924.
38. Lee S, Varvel NH, Konerth ME, et al. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. *Am J Pathol*. 2010;177:2549-2562.
39. Pabon MM, Bachstetter AD, Hudson CE, Gemma C, Bickford PC. CX3CL1 reduces neurotoxicity and microglial activation in a rat model of Parkinson's disease. *J Neuroinflammation*. 2011;8:9.
40. Rogers JT, Morganti JM, Bachstetter AD, et al. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *J Neurosci*. 2011;31:16241-16250.
41. Kosloski LM, Kosmacek EA, Olson KE, Mosley RL, Gendelman HE. GM-CSF induces neuroprotective and anti-inflammatory responses in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine intoxicated mice. *J Neuroimmunol*. 2013;265:1-10.
42. Olmos-Alonso A, Schetters ST, Sri S, et al. Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. *Brain*. 2016;139:891-907.
43. Dagher NN, Najafi AR, Kayala KM, et al. Colony-stimulating factor 1 receptor inhibition prevents microglial plaque association and improves cognition in 3xTg-AD mice. *J Neuroinflammation*. 2015;12:139.
44. Luo P, Chu SF, Zhang Z, Xia CY, Chen NH. Fractalkine/CX3CR1 is involved in the cross-talk between neuron and glia in neurological diseases. *Brain Res Bull*. 2019;146:12-21.
45. Pons V, Rivest S. New therapeutic avenues of mCSF for brain diseases and injuries. *Front Cell Neurosci*. 2018;12:499.
46. Galambos A, Szabo E, Nagy Z, et al. A systematic review of structural and functional MRI studies on pain catastrophizing. *J Pain Res*. 2019;12:1155-1178.
47. Bjurström MF, Bodelsson M, Irwin MR, Orbjörn C, Hansson O, Mattsson-Carlgren N. Decreased pain sensitivity and alterations of cerebrospinal fluid and plasma inflammatory mediators after total hip arthroplasty in patients with disabling osteoarthritis. *Pain Pract*. 2022;22:66-82.
48. Meyer PF, Labonté A, Rosa-Neto P, Poirier J, Breitner JCS. No apparent effect of naproxen on CSF markers of innate immune activation. *Ann Clin Transl Neurol*. 2019;6:1127-1133.
49. Lavand'homme PM, Kehlet H, Rawal N, Joshi GP. Pain management after total knee arthroplasty: PROcedure SPEcific Postoperative Pain ManagemenT recommendations. *Eur J Anaesthesiol*. 2022;39:743-757.

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