The central sensitization inventory predict pain-related disability for musculoskeletal disorders in the primary care setting

Tanaka, Katsuyoshi

(Degree)
博士（保健学）

(Date of Degree)
2020-03-25

(Date of Publication)
2021-03-01

(Resource Type)
doctoral thesis

(Report Number)
甲第7752号

(URL)
https://hdl.handle.net/20.500.14094/D1007752

博 士 論 文

The central sensitization inventory predict pain-related disability for musculoskeletal disorders in the primary care setting

（中枢性感作票はプライマリーケアにおける

筋骨格系障害の疼痛関連能力障害を予測する）

令和 2 年 1 月 15 日

神戸大学大学院保健学研究科保健学専攻

Katsuyoshi Tanaka
田中　克宜

Abstract

Background: Central sensitization (CS) is found in patients with musculoskeletal disorders and is related to clinical symptoms, including pain-related disability. The Central Sensitization Inventory (CSI) has been developed for patients who are at risk of symptoms related to CS, and CSI severity levels are suggested for clinical interpretation of the CSI score. However, the longitudinal relationship between CSI severity and pain-related disability is unclear in primary care. In this study, we investigated the association between CSI severity levels and the profiles of patients with musculoskeletal disorders as well as the longitudinal relationship between CSI severity levels and pain-related disability in primary care settings.

Methods: A total of 553 patients were assessed using CSI, EuroQol-5 dimension (EQ5D), and Brief Pain Inventory (BPI). Of the 553 patients, 150 patients were reassessed at the 3-month follow-up. Patients were grouped into three severity levels according to baseline CSI score: subclinical, mild, and moderate to higher level.

Results: As the CSI severity levels increased, the clinical symptoms tended to worsen on cross-sectional analysis ($p<0.05$). Pain-related disability at the 3-month follow-up was significantly higher for patients with moderate to high baseline CSI severity levels than for patients with subclinical baseline CSI levels ($p<0.001$). Furthermore, pain-related

disability increased according to the CSI severity level, with a medium to large effect size. However, there were no differences in pain duration across the CSI severity levels.

Conclusions: CSI has clinical utility as a prediction tool regardless of pain duration in patients with musculoskeletal disorders in primary care settings.

Significance: Higher CSI severity levels predicted higher pain-related disability for patients with musculoskeletal disorders in a primary care setting. CSI is a clinically useful prediction tool in patients with musculoskeletal disorders.

This paper published in European Journal of Pain (doi: 10.1002/ejp.1443).

The title is “The central sensitization inventory predict pain-related disability for musculoskeletal disorders in the primary care setting.”

1. INTRODUCTION

Musculoskeletal disorders constitute a huge global health problem, leading to substantial economic and human costs and adverse effect on the quality of life (QOL) (Itoh, Kitamura, & Yokoyama, 2013; Kovacs, Abraira, Zamora, Fernández, & Spanish Back Pain Research Network, 2005; Mousavi et al., 2011). In patients with musculoskeletal disorders, pain-related disability is one of the most important outcomes and key for pain management and treatment (Lin et al., 2011; Marshall, Schabrun, & Knox, 2017; Schulz et al., 2015). Pain-related disability includes activity limitations and participation restrictions induced by pain. Therefore, appropriate assessments of factors for pain-related disability are required to manage musculoskeletal pain in primary care setting. In addition, identifying patients at high risk of severe pain-related disability in a primary care setting is crucial for disease prevention and avoidance of surgery.

Central sensitization (CS) is defined as the increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input (Loeser & Treede, 2008). Although a gold standard is lacking, Quantitative Sensory Testing (QST) is commonly used for evaluating CS symptoms, and CS is found in many chronic musculoskeletal pain disorders (Lluch, Torres, Nijs, & Oosterwijck, 2014;

Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998; van Wilgen, Konopka, Keizer, Zwerver, & Dekker, 2013; Yunus, 2007). However, the CS phenomenon was also found in patients with acute pain (Dirks, Møiniche, Hilsted, & Dahl, 2002; Woolf, 2011), which indicates that studies on CS should examine patients with acute and chronic pain. Previous studies had shown the association between measures of QST and disability (Coombes, Bisset, & Vicenzino, 2012; Farasyn & Meeusen, 2005; Johnston, Jull, & Souvlis, 2008). However, it was difficult to interpret the results because the correlations may depend on the site of testing, type of stimulation (e.g., mechanical, thermal), and outcome measured (e.g., threshold, tolerance, temporal summation) (Hübscher et al., 2013). Furthermore, QST lacks feasibility for clinical practice because of its cost and time-consuming protocols.

Given the lack of feasibility for clinical practice, the Central Sensitization Inventory (CSI) has been developed (Mayer et al., 2012). The CSI is a symptomatological and self-reported questionnaire for patients who are at a high risk of symptoms related to CS. The CSI score is related to widespread pain index, pain intensity, disability, QOL and pain catastrophization (Kregel et al., 2018; van der Noord, Paap, & Wilgen, 2018). More recently, CSI severity levels are suggested for clinical interpretation, which are associated

with clinical symptoms (Neblett, Hartzell, Mayer, Cohen, & Gatchel, 2017). However, most of the previous studies were cross-sectional, and the longitudinal relationship has been investigated only through surgery by dichotomizing participants at cut-off score (Bennett, Walsh, Thompson, & Krishnaner, 2017; Kim, Yoon, Yoon, Yoo, & Ahn, 2015). As a stratified approach by use of prognostic screening with matched pathways was more effective for disability than usual care in primary care (Hill et al., 2011), it is meaningful to examine whether the CSI score at baseline predicts poor outcomes in a primary care setting. Therefore, this study aimed to investigate the association between CSI severity levels and profiles of patients with musculoskeletal disorders, including acute/chronic pain in a primary care setting, and to investigate the longitudinal relationship between CSI severity levels and pain-related disability in these populations.

2. METHODS

2.1 Study design

Patients with musculoskeletal disorders who started receiving physical therapy from November 2015 to August 2017 were recruited from an orthopedic clinic. A total of 584 were assessed for eligibility. The inclusion criteria were having musculoskeletal pain and age between 20 and 80 years. Of the total sample, 31 patients were eliminated based

on the following exclusion criteria: (1) diagnosis of cancer, brain or spinal cord injury, neurological disease, and dementia (n = 17) and/or (2) poor Japanese language comprehension (n = 14). The remaining 553 patients were assessed at baseline. If patients did not receive treatment at 3-month follow-up, we conducted reassessment by mail. Patients eligible for follow-up were those who did not continue treatment and replied to the mail, and those who continued the treatment. Of the 553 patients, 150 patients were interviewed again 3 months after the baseline assessment. They received general physical therapy (stretch, muscle strength exercise and aerobic exercise) 1–3 times a week. Patients who received therapy less than four times were excluded from the prospective analyses to exclude patients with only minor illness.

Ethical approval was obtained from the Institutional Ethics Committee of Konan Women's University. All participants provided written informed consent before participating in the study. The study was conducted in accordance with principles of the Declaration of Helsinki.

2.2 Measures

After the participants signed the informed consent form, sociodemographic data (age, sex, height and weight) and data on pain duration were obtained by questionnaire survey, and all participants filled out the following questionnaires: CSI, Brief Pain Inventory (BPI) and EuroQol-5 dimension (EQ5D).

2.2.1 Central sensitization inventory

The CSI consists of two parts. Part A includes 25 items about CS-related symptoms (Mayer et al., 2012). Each item is scored from 0 to 4, with higher total scores reflecting higher CS symptomatology. A systematic review revealed that CSI has strong psychometric properties (Scerbo et al., 2018), and the Japanese version of CSI demonstrated strong psychometric properties (test‑retest reliability = 0.85; Cronbach's alpha = 0.89) (Tanaka et al., 2017). Recently, five severity levels (subclinical = 0‑29; mild = 30‑39; moderate = 40‑49; severe = 50‑59; and extreme = 60‑100) have been developed to help in the clinical interpretation of the CSI (Neblett et al, Hartzell, Mayer, et al., 2017). Part B asks whether patients have previously been diagnosed with seven specific central sensitivity syndrome (CSS) diagnoses or three CSS-related disorders. The CSI has been translated into Japanese and validated (Tanaka et al., 2017).

2.2.2 Brief pain inventory

The BPI is a self-reported questionnaire assessing pain intensity and pain interference (Cleeland & Ryan, 1994). It consists of two subscales, which include four pain severity and seven pain interference items with an 11-point scale (0 = no and 10 = worst (completely)). The scores for pain intensity and pain interference were obtained by averaging all item scores in each subscale. In this study, the pain interference score was used as the score of pain-related disability, which is the outcome of the prospective analysis. The validity and clinical utility of BPI has been evaluated for several disorders (Dworkin et al., 2008; Keller et al., 2004; Mendoza et al., 2012). The Japanese version of the BPI used in this study has been validated (Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998).

2.2.3 EuroQol-5 dimension

The EQ5D was developed as an instrument that is not specific to disease but is standardized and can be used as a complement to existing health-related QOL measures

(Rabin & de Charro, 2001). It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients are asked to indicate on a three-point scale in each dimension, which can generate a single index value for patients' health state. These values are expressed in numbers, which range from 0 (dead) to 1 (full health). Tsuchiya et al. showed the Japanese value set (Tsuchiya et al., 2002).

2.3 Statistical analyses

We grouped the participants into three severity levels according to their total CSI score at baseline (0–29, subclinical; 30–39, moderate; ≥40, moderate to higher level) with reference to a previous study (Neblett, Hartzell, Mayer, et al., 2017). In the cross-sectional analysis, the relationships between clinical information at baseline and CSI severity levels were evaluated using the Jonckheere-Terpstra trend test for continuous variables (EQ5D, pain intensity and pain-related disability from BPI). The Jonckheere-Terpstra test is a non-parametric test that assesses whether there are linear increasing or decreasing trends in the clinical symptoms across the three CSI severity levels. In addition, the chi-square test for the trend of categorical variables was used to compare the diagnosis history of

CSS (no CSS, one CSS, two or more CSS) according to the CSI severity levels (Sribney, 2003). These trend tests were conducted based on the hypothesis that higher CSI severity levels would have worse clinical characteristics. Regarding participants' sociodemographic information, differences according to the CSI severity levels were assessed using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Fisher's exact test was used if the expected count in any cell was <10. When the significance level was $p < 0.05$ by the Kruskal-Wallis test, the Mann-Whitney U test was used for post-hoc comparison. A significance level of $p < 0.017$ ($\alpha < 0.05/3$) was set (Bonferroni correction was applied to compensate for the multiple testing problem). Moreover, we evaluated the relationships between clinical characteristics (EQ5D and pain intensity from BPI) and CSI severity levels with stratification for pain duration (< 3 months or ≥ 3 months) using the Jonckheere-Terpstra trend test in the cross-sectional analysis. Furthermore, we completed linear regression models, with pain-related disability from BPI as the dependent variable and CSI severity levels as the independent variable (crude model). Subsequently, the model adjusting for sociodemographic characteristics (age, sex, height, and weight) and clinical characteristics (duration category, pain intensity, and diagnosis history of CSS)

was obtained (adjusted model). In both models, subclinical was a reference to mild and moderate to higher level.

In the prospective analyses, participants' characteristics were compared using Mann-Whitney U test between participants who were and those who were not assessed at follow-up. To assess the relationship between the CSI and pain-related disability, we completed linear regression models, with pain-related disability at 3-month follow-up as the dependent variable and CSI severity levels at baseline as the independent variable (crude model). To consider the influence of confounding factors, we created an adjusted model that controls for sociodemographic and clinical characteristics (duration category, pain intensity at baseline, pain-related disability at baseline, diagnosis history of CSS, and number of treatments). In addition, multivariate linear regression was performed in patients with acute pain and in all participants, but it was not performed in patients with chronic pain because of insufficient sample size. Furthermore, standardized mean difference effect size (Cohen's *d*) was calculated for pairwise comparisons (subclinical vs. mild or moderate to higher) of pain-related disability at baseline and 3-month follow-up. Cohen's *d* indicates the magnitude of effect without dependence on the sample size.

Cohen's *d* represents small (0.20 = groups' means differ 0.2 standard deviations), medium (0.50), and large (0.80) up to huge (2.0) effects (Cohen, 1998). All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). Beta coefficients and 95% confidence interval were calculated by linear regression models. Statistical significance was set at 0.05 except for Bonferroni correction.

3. RESULTS

3.1 Participants

Participants with subclinical, mild and moderate to higher CSI levels were 418 (75.6%), 83 (15.0%), and 52 (9.4%), respectively. A flowchart of the study is presented in Figure 1. Of the 553 patients, 403 were excluded because of unfeasible follow-up assessment and 12 for insufficient number of treatments (<4 times), leaving 138 participants for analyses at 3-month follow-up. Of the 138 participants who were included in the prospective analyses, 109 participants (79.0%) had subclinical, 13 participants (9.4%) had mild and 16 participants (11.6%) had moderate to higher CSI severity levels at baseline.

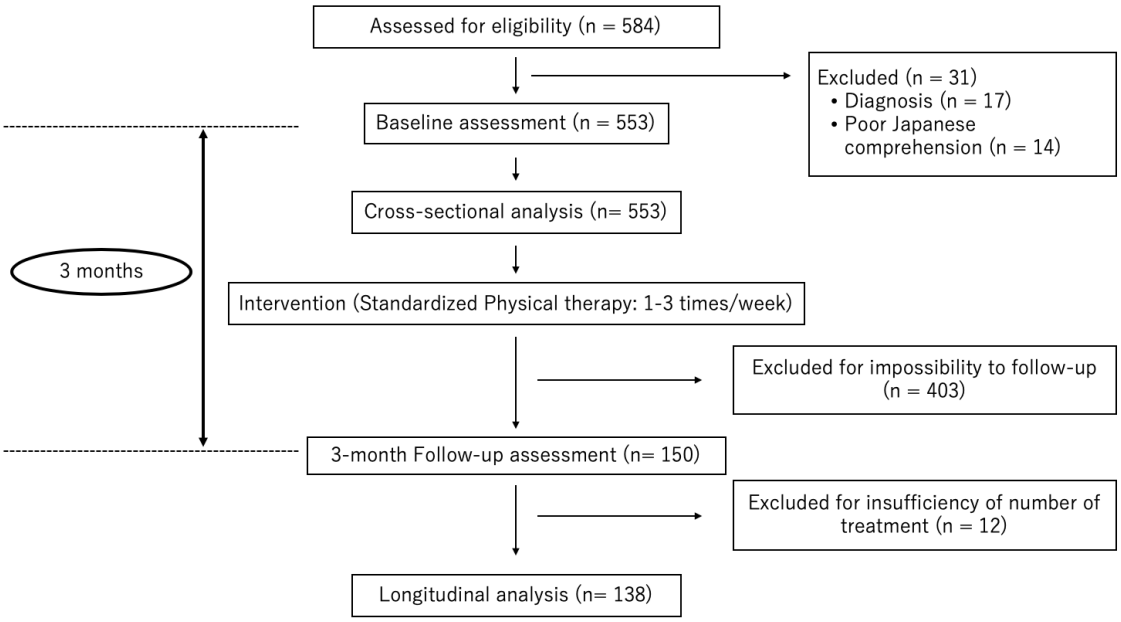

FIGURE 1. Flow diagram of this study

3.2 Cross-sectional analysis

The mean CSI scores of each severity level were as follows: subclinical, 15.7 ± 7.2; mild, 33.4 ± 2.5; moderate to higher, 48.8 ± 9.3. Table 1 presents the sociodemographic and clinical characteristics at baseline according to the CSI severity levels. Because only a few participants had a high score, we used the CSI severity levels with three levels, with reference to CSI severity levels of five levels (Neblett, Hartzell, Mayer, et al., 2017). In the cross-sectional analysis, we found a significant difference in the proportion of female participants between the CSI severity levels (subclinical, 62.7%; mild, 79.5%; moderate to higher, 69.2%; $\chi^2(2) = 9.02$; p=0.011). Participants in the subclinical CSI severity group were significantly heavier than those in the mild CSI severity group (60.3 kg vs. 56.1 kg, $p = 0.005$). Trend analyses showed that participants with higher CSI severity levels had significantly lower score in the EQ5D and higher score in pain intensity and pain-related disability and were more likely to have diagnosis history of CSS (all $p < 0.001$). In the cross-sectional analysis, 383 participants with acute pain and 170 participants with chronic pain indicated similar trends of clinical symptoms according to the CSI severity: The median scores were as follows: EQ5D [acute: from 0.768 (subclinical) to 0.596 (moderate to higher); chronic: from 0.768 (subclinical) to 0.661 (moderate to higher)], pain intensity [acute: from 2.3 (subclinical) to 3.6 (moderate

to higher); chronic: from 2.8 (subclinical) to 4.4 (moderate to higher)], and pain-related disability [(acute: from 1.6 (subclinical) to 5.1 (moderate to higher); chronic: from 1.6 (subclinical) to 4.7 (moderate to higher)] (all $p < 0.001$). A cross-sectional relationship between the CSI severity levels and pain-related disability is shown in Table 2. After adjustment, pain-related disability scores in mild and moderate to higher CSI severity levels were significantly higher than those in the subclinical CSI severity level [subclinical: 2.0 ± 1.8 (mean ± SD); mild: 3.4 ± 2.3 (mean ± SD); beta coefficients, 0.666; 95%CI, 0.278 to 1.054; $p = 0.001$; moderate to higher: 4.9 ± 2.2 (mean ± SD); beta coefficients, 1.894; 95%CI, 1.405 to 2.383; $p < 0.001$]. In addition, pain-related disability score increased with mild CSI severity group (mean ± SD, from 2.0 ± 1.8 to 3.4 ± 2.3; effect size = 0.71) and moderate to higher CSI severity group (mean ± SD, from 2.0 ± 1.8 to 4.9 ± 2.2; effect size = 1.54). The effect size was indicated as “medium” and “large.”

Table 1. Baseline characteristics pf the patients

	Cross-sectional analysis (n = 553)			
	Subclinical[1] (n = 418)	Mild[2] (n = 83)	Moderate to higher[3] (n = 52)	*p*
Age	52.6 ± 14.8	53.5 ± 15.6	48.9 ± 14.4	0.167
Sex (n (%))	262 (62.7)	66 (79.5)	36 (69.2)	0.011
Height (cm)	162.2 ± 9.0	160.0 ± 7.1	162.1 ± 7.8	0.169
Weight (kg)	60.3 ± 12.8[2]	56.1 ± 9.0[1]	59.3 ± 12.6	0.018
Disease site (n (%))				
Neck	75 (17.9)	17 (20.5)	10 (19.2)	
Shoulder	71 (17.0)	12 (14.5)	5 (9.6)	
Lumbar	153 (36.6)	31 (37.3)	19 (36.5)	0.571
Knee	66 (15.8)	15 (18.1)	7 (13.5)	
Others	53 (12.7)	8 (9.6)	11 (21.2)	
Pain duration (w)	18.8 ± 47.9	26.4 ± 63.8	45.8 ± 106.6	0.581
CSI score[a]	16.0 (10.0)	33.0 (4.0)	46.5 (9.8)	<0.001*
CSS (n (%))				
no CSS	333 (79.7)	48 (57.8)	23 (44.2)	
1 CSS	68 (16.3)	25 (30.1)	14 (26.9)	<0.001 †
2+ CSSs	17 (4.0)	10 (12.1)	15 (28.9)	
EQ5D[a]	0.768 (0.080)	0.661 (0.130)	0.603 (0.220)	<0.001*
Pain intensity[a]	2.5 (2.0)	3.5 (2.3)	4.1 (2.4)	<0.001*
Pain-related disability[a]	1.6 (2.2)	3.4 (3.6)	5.0 (3.5)	<0.001*

Table 1. Continued

	Longitudinal analysis (n = 138)			
	Subclinical[1] (n = 109)	Mild[2] (n = 13)	Moderate to higher[3] (n = 16)	*p*
Age	56.7 ± 14.0	63.0 ± 12.8[3]	47.7 ± 16.2[2]	0.023
Sex (n (%))	76 (69.7)	8 (61.5)	11 (68.8)	0.802
Height (cm)	160.0 ± 8.8	160.4 ± 7.8	162.8 ± 7.8	0.537
Weight (kg)	58.7 ± 12.1	53.6 ± 9.3	55.9 ± 10.1	0.275
Disease site (n (%))				
Neck	19 (17.4)	1 (7.6)	3 (18.7)	
Shoulder	21 (19.3)	4 (30.8)	1 (6.3)	
Lumbar	36 (33.0)	4 (30.8)	8 (50)	0.337
Knee	22 (20.2)	4 (30.8)	1 (6.3)	
Others	11 (10.1)	0 (0)	3 (18.7)	
Pain duration (w)	12.8 ± 23.7	7.2 ± 10.2	19.6 ± 37.5	0.749
CSI score[a]	16.0 (11.0)	34.0 (5.5)	43.5 (7.0)	<0.001*
CSS (n (%))				
no CSS	85 (78.1)	9 (69.2)	11 (68.7)	
1 CSS	15 (13.8)	1 (7.7)	1 (6.3)	0.094 †
2+ CSSs	9 (8.3)	3 (23.1)	4 (25.0)	
EQ5D[a]	0.768 (0.120)	0.649 (0.080)	0.592 (0.230)	<0.001*
Pain intensity[a]	2.5 (2.0)	4.0 (1.5)	3.9 (2.3)	<0.001*
Pain-related disability[a]	1.9 (3.1)	3.7 (4.3)	5.3 (4.0)	<0.01*

Values are numbers and percent values for categorical variables and mean and SD for continuous variables unless otherwise indicated. Superscript letters indicate which groups significantly differed from each other in post-hoc comparison. CSI, Central Sensitization Inventory; CSS, Central Sensitivity Syndrome; EQ5D, EuroQol-5 dimension.

[a] Displayed as median (interquartile range); * Assessed by Jonckheere-Tepstra trend test; † Assessed by Chi-square test for the trend

3.3 Prospective analyses

There were no significant differences in participants' characteristics according to whether they were assessed at follow-up (n = 138) or not assessed (n = 415) (all p > 0.05). The mean CSI scores of each severity levels were as follows: subclinical, 15.9 ± 7.3; mild, 34.2 ± 3.0; moderate to higher, 45.9 ± 7.8. In the prospective analysis, the participants in the mild CSI severity group were significantly older than those in the moderate to higher CSI severity group (mean age, 63.0 years vs. 47.7 years). The trend analysis showed that participants with higher CSI severity levels had significantly lower scores in the EQ5D and higher scores in pain intensity and pain-related disability (all p < 0.001). However, there was no significant trend in the number of diagnosis histories of CSS (p = 0.094). A longitudinal relationship between CSI severity levels and pain-related disability at 3-month follow-up is shown in Table 2. After adjustment, the pain-related disability score at 3-month follow-up was significantly higher in the moderate to higher CSI severity group according to the CSI severity levels at baseline than that of the subclinical CSI severity group [B (95%CI) = 1.674 (0.852 to 2.442), p < 0.001]. It indicated that pain-related disability score increased by 1.674, 95%CI from 0.852 to 2.442, in accordance with the CSI severity levels that increased from subclinical to moderate to higher level. In addition, a similar result was shown in the analysis of 96 participants with acute pain [adjusted model; moderate to higher, B (95%CI) = 2.032 (1.010 to 3.053), p <

0.001]. Furthermore, the pain-related disability score increased according to the CSI severity levels (mild, mean ± SD: from 2.3 ± 2.0 to 3.7 ± 2.3, effect size = 0.41; moderate to higher, mean ± SD: from 2.3 ± 2.0 to 4.6 ± 2.1, effect size = 1.57, respectively). The effect size indicated “medium” and “large.”

Table 2. The relationships between CSI severity levels and pain-related disability

	Pain-related disability (Mean ± SD)	*d*	**Cross-sectional (n=553) *** Crude B (95%CI)	*p*	Adjusted B (95%CI)	*p*
CSI severity levels						
Subclinical	2.0 ± 1.8		Ref.		Ref.	
Mild	3.4 ± 2.3	0.71	1.349 (0.894 to 1.804)	< 0.001	0.666 (0.278 to 1.054)	0.001
Moderate to higher	4.9 ± 2.2	1.54	2.870 (2.313 to 3.427)	< 0.001	1.894 (1.405 to 2.383)	< 0.001
Adjusted R^2			0.179		0.461	

	Pain-related disability (Mean ± SD)	*d*	**Longitudinal (n=138) †** Crude B (95%CI)	*p*	Adjusted B (95%CI)	*p*
CSI severity levels						
Subclinical	2.3 ± 2.0		Ref.		Ref.	
Mild	3.7 ± 2.3	0.41	0.492 (-0.333 to 1.316)	0.240	0.013 (-0.832 to 0.858)	0.976
Moderate to higher	4.6 ± 2.1	1.57	2.173 (1.421 to 2.925)	< 0.001	1.674 (0.852 to 2.442)	< 0.001
Adjusted R^2			0.184		0.256	

95%CI, 95% confidence interval; d, Cohen's d, versus subclinical; CSI, Central Sensitization Inventory. Adjusted for age, sex, height, weight, duration category (acute or chronic), pain intensity at baseline, pain interference at baseline (only longitudinal), number of treatment (only longitudinal), and diagnosis history of CSS.

* Dependent variable was pain interference at baseline

† Dependent variable was pain interference at 3-month follow-up

4. DISCUSSION

This study confirmed the relationship between CSI severity levels and clinical symptoms in patients with musculoskeletal disorders in a primary care setting, including acute and chronic phase. As the CSI severity levels increased, the clinical symptoms tended to get worse in the cross-sectional analysis. In addition, the high CSI severity levels predicted high pain-related disability at 3-month follow-up, with medium to large effect size. However, there were no significant differences in pain duration through the CSI severity levels, and the relationship between the CSI severity levels and clinical symptoms in patients with acute pain was the same with that of patients with chronic pain. Therefore, the CSI has clinical utility as a prediction tool regardless of pain duration in patients with musculoskeletal disorders in a primary care setting.

As the CSI severity levels increased, the clinical symptoms tended to get worse. These results support previous studies which reported that the CSI score/severity levels correlate with disability, QOL, and pain intensity (Kregel et al., 2018; Neblett, Hartzell, Mayer, et al., 2017). Examination using CSI severity levels was more useful to interpret CS-related symptoms than examination using a cut-off score. A cut-off score of 40 was not described to be diagnostic, but with this score, the CSI was able to best distinguish

subjects with CSS from the non-patient population (Neblett et al., 2013). In addition, a previous study showed a migraine-specific CSI cut-off score of 22.5 (Aguila et al., 2016), which indicates that applying cut-off points needs consideration. Therefore, the findings suggest that clinicians should evaluate patients by CSI severity levels in addition to any CSI cut-off point.

A high CSI severity level affected pain-related disability at 3-month follow-up. This indicated that the CSI has a predictive ability of clinical outcome in a primary care setting. Previous studies reported that preoperative CSI total score predicts poor long-term postoperative outcomes (Bennett, Walsh, Thompson, & Krishnaney, 2017; Kim et al., 2015). The comparison of outcomes in these studies was conducted using 40 points as the CSI score cut-off value. Thus, it was consistent with our finding that moderate to higher CSI severity levels (≥40 points) at baseline predicted higher pain-related disability at 3-month follow-up. In addition, the present study is the first to examine the predictive ability of the CSI in a primary care setting. Therefore, additional treatment for patients with high CSI scores was suggested, and our findings supported those of a previous study that showed that a 2-week function restoration program, which involves not only physical training but also education and counseling, improved CS-related patient-reported

symptoms, including pain intensity, depressive symptoms, and perceived disability in chronic spinal pain disorder (Neblett, Hartzell, Williams, et al., 2017). Furthermore, the result suggested a large effect size for moderate to higher CSI score. Therefore, the CSI has clinical utility as a predictive tool. These findings help clinicians to make decisions for treatment strategies.

There were no significant differences in pain duration through the CSI severity levels. In patients with acute pain, CSI severity levels were related to clinical symptoms and pain-related disability at 3-month follow-up. This result suggested that clinical symptoms were affected by CS-related symptoms even in short-term pain with duration less than 3 months. Some previous studies focused on CS in the acute phase, such as postoperative incisional pain associated with a secondary punctate hyperalgesia that is ketamine sensitive (Stubhaug, Breivik, Eide, Kreumen, & Foss, 1997), and CS may contribute to some aspects of postoperative pain (Dirks et al., 2002). These indicated the possibility that CS was induced in the acute phase. In addition, many items on the CSI are common elements of anxiety and depressive disorders. These conditions may have contributed to the CS-related symptoms. Then, Klyne et al. have shown that CS during the acute phase was resolved in many cases, and it is a precursor to the transition to

chronicity when combined with other psychological features (Klyne, Moseley, Sterling, Barbe, & Hodges, 2019). Notably, there is no set of CS-defining criteria established in the literature. Therefore, factors other than pain duration may contribute to the CS-related symptoms. Further, this study showed that CSI had clinical application as a predictive tool regardless of pain duration.

As the major strength of this study, we showed the higher CSI severity levels predicted higher pain-related disability of patients with musculoskeletal disorders in the primary care setting. Furthermore, we showed the clinical utility of the CSI as a prediction tool regardless of pain duration and type of diagnosis. This suggests that the conclusion of this study can be generalized to patients with musculoskeletal disorders.

Several limitations of our study should be considered. First, there were 553 patients at baseline assessment, which decreased to 138 patients at follow-up assessment, indicating the possibility of selection bias and patients with only minor illness were satisfied with treatment in the short term. Patients eligible for follow-up were those who did not continue treatment and replied to the mail, and those who continued the treatment. That is, it was possible that patients who recovered were not followed. Most of the

patients who were not followed up were grouped into the subclinical group at baseline (74.5%, 309 of 415 patients), which might underestimate the predictive ability of CSI severity levels. However, pain-related disability at the 3-month follow-up was significantly higher for patients with a moderate to higher CSI severity level than for those with subclinical level at baseline. In addition, no significant differences were found in participants' characteristics according to whether they were assessed at follow-up. Although we have reassessed by mail whether patients completed the treatments within 3 months, it is not known, nor possible to evaluate, why many patients did not response to the mail. Furthermore, even if the insufficiency of follow-up assessment was a limitation in regular clinical practice, the results in regular clinical practice indicated the importance of the clinical utility of CSI scores. Second, there was disproportion in the number of patients between severity levels in the linear regression model of the prospective analysis. However, our model indicated that the effect of the number of events per variable (EPV) was 11.5, with a total of 138 patients and 12 independent variables. EPV values less than 10 can lead to major problems (Peduzzi, Concato, Feinstein, & Holford, 1995; Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). In addition, we estimated the effect size, which was not affected by the sample size. It indicated that the CSI severity levels had beneficial effect on pain-related disability 3 months later. Finally,

this study used few variables of clinical symptoms. However, we showed the longitudinal relationship between CSI score and pain-related disability with the regression model adjusted for confounding factors. The relationships between CSI and somatosensory function measured by QST and psychosocial factors are still unknown in this population. Therefore, further studies that include more variables and examine the relationship with CSI will be required.

5. Conclusions

Our results revealed that the higher CSI severity levels predicted higher pain-related disability at 3-month follow-up of patients with musculoskeletal disorders in the primary care setting. The CSI is a clinically useful prediction tool regardless of pain duration in patients with musculoskeletal disorders in a primary care setting.

ACKKNOWLEDGEMENTS

I would like to thank Dr. Ono Rei, Kobe University, Graduate School of Health Sciences, for his help in contributing to the conception and design of the study and providing feedback to the implementation of the study. I would also like to thank Dr. Tomohiko Nishigami, Department of Physical Therapy, Faculty of Health and Welfare,

Prefectural University of Hiroshima, for his help in providing feedback to the implementation of the study. Finally, I would like to thank other researchers, the staff members, and all other people involved in this study. This study was supported by JSPS KAKENHI Grant Number JP17K01543.

CONFLICT OF INTEREST

The authors declared no potential conflict of interests, with respect to the research, authorship, and/or publication of this article.

REFERENCES

Aguila, M.R., Rebbeck, T., Leaver, A. M., Lagopoulos, J., Brennan, P. C., Hübscher, M., Refshauge, K.M. (2016). The association between clinical characteristics of migraine and brain GABA levels: an exploratory study. *The Journal of Pain, 17,* 1058-1067. https://doi.org/10.1016/j.jpain.2016.06.008

Bennett, E. E., Walsh, K. M., Thompson, N. R., Krishnaney, A. A. (2017). Central Sensitization Inventory as a predictor of worse quality of life measures and increased length of stay following spinal fusion. *World Neurosurgery*, *104*, 594-600. https://doi.org/10.1016/j.wneu.2017.04.166

Cleeland, C. S., Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain

Inventory. *Academy of Medicine, Singapore, 23*, 129-138.

Cohen, J. (1998). *Statistical power analysis for the behavioral sciences*. New York, NY: Routledge Academic.

Coombes, B. K., Bisset, L., Vicenzino, B. (2012). Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia. *The Clinical Journal of Pain*, 28, 595-601. https://doi.org/10.1097/AJP.0b013e31823dd333

Dirks, J., Møiniche, S., Hilsted, K. L., Dahl, J. B. (2002). Mechanisms of postoperative pain: clinical indications for a contribution of central neuronal sensitization. *Anesthesiology*, *97*, 1591-1596.

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., …Zavisic, S. (2008). Interpreting the clinical Importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain*, *9*, 105-121. https://doi.org/10.1016/j.jpain.2007.09.005

Farasyn, A., Meeusen, R. (2005). The influence of non-specific low back pain on pressure pain thresholds and disability. *European Journal of Pain*, *9*, 375-381. https://doi.org/10.1016/j.ejpain.2004.09.005

Hill, J. C., Whitehurst, D. G., Lewis, M., Bryan, S., Dunn, K. M., Foster, N. E.,…Hay, E. M. (2011). Comparison of stratified primary care management for low back pain with

current best practice (STarT Back): a randomized controlled trial. *Lancet, 378,* 1560-1571. https://doi.org/10.1016/S0140-6736(11)60937-9

Hübscher, M., Moloney, N., Leaver, A., Rebbeck, T., McAuley, J. H., Refshauge, K. M. (2013). Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. *Pain*, *154,* 1497-1504. https://doi.org/10.1016/j.pain.2013.05.031

Itoh, H., Kitamura, F., Yokoyama, K. (2013). Estimates of annual medical costs of work-related low back pain in Japan. *Industrial Health*, *51,* 524-529.

Johnston, V., Jimmieson, N. L., Jull, G., Souvlis, T. (2008). Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. *Pain*, *15,* 257-265. https://doi.org/10.1016/j.pain.2007.08.037

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *The Clinical Journal of Pain*, *20*, 309-318.

Kim, S. H., Yoon, K. B., Yoon, D. M., Yoo, J. H., Ahn, K. R. (2015). Influence of centrally mediated symptoms on postoperative pain in osteoarthritis patients undergoing total knee arthroplasty: a prospective observational evaluation. *Pain Practice*, 15, E46-53. https://doi.org/10.1111/papr.12311

Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. (2019). Are signs of central sensitisation in acute low back pain a precursor to poor outcomes? *The Journal of Pain*, https://doi.org/10.1016/j.jpain.2019.03.001.

Kovacs, F. M., Abraira, V., Zamora, J., Fernández, C.; Spanish Back Pain Research Network. (2005). The transition from acute to subacute and chronic low back pain: a study based on determinants of quality of life and prediction of chronic disability. *Spine (Phila Pa 1976)*, *30*, 1786-1792.

Kregel, J., Schumacher, C., Dolphenes, M., Malfliet, A., Goubert, D., Lenoir, D.,…Coppieters, I. (2018). Convergent validity of the Dutch Central Sensitization Inventory: associations with psychophysical pain measures, quality of life, disability, and pain cognitions in patients with chronic spinal pain. *Pain Practice*, *18,* 777-787. https://doi.org/10.1111/papr.12672

Lin, C. W., McAuley, J. H., Macedo, L., Barnett, D. C., Smeets, R. J., Verbunt, J. A. (2011). Relationship between physical activity and disability in low back pain: a systematic review and meta-analysis. *Pain*, *152,* 607-613. https://doi.org/10.1016/j.pain.2010.11.034

Lluch, E., Torres, R., Nijs, J., Van Oosterwijck, J. (2014). Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *European*

Journal of Pain, 18, 1367-1375. https://doi.org/10.1002/j.1532-2149.2014.499.x

Loeser, J. D., Treede, R. D. (2008). The Kyoto protocol of IASP Basic Pain Terminology. *Pain*, *137,* 473-477. https://doi.org/10.1016/j.pain.2008.04.025

Maixner, W., Fillingim, R., Sigurdsson, A., Kincaid, S., Silva, S. (1998). Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. *Pain, 76,* 71-81.

Marshall, P. W. M., Schabrun, S., Knox, M. F. (2017). Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. *PLoS One*, *12*, e0180788. https://doi.org/10.1371/journal.pone.0180788

Mayer, T. G., Neblett, R., Cohen, H., Howard, K. J., Choi, Y. H., Williams, M. J.,…Gatchel, R. J. (2012). The development and psychometric validation of the central sensitization inventory. *Pain Practice*, *12*, 276-285. https://doi.org/10.1111/j.1533-2500.2011.00493.x

Mendoza, T. R., Koyyalagunta, D., Burton, A. W., Thomas, S. K., Phan, M. H., Giralt, S. A., Shah, J. J., Cleeland, C. S. (2012). Changes in pain and other symptoms in patients with painful multiple myeloma-related vertebral fracture treated with kyphoplasty or vertebroplasty. *J Pain*, 13, 564-570. https://doi.org/10.1016/j.jpain.2012.03.003

Mousavi, S. J., Akbari, M. E., Mehdian, H., Mobini, B., Montazeri, A., Akbarnia, B., Parnianpour, M. (2011). Low back pain in Iran: a growing need to adapt and implement evidence-based practice in developing countries. *Spine (Phila Pa 1976)*, 36, E638-646. https://doi.org/10.1097/BRS.0b013e3181fa1da2

Neblett, R., Cohen, H., Choi, Y., Hartzell, M. M., Williams, M., Mayer, T. G., Gatchel, R. J. (2013). The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *The Journal of Pain*, 14, 438-445. https://doi.org/10.1016/j.jpain.2012.11.012

Neblett, R., Hartzell, M. M., Mayer, T. G., Cohen, H., Gatchel, R. J. (2017a). Establishing clinically relevant severity levels for the central sensitization inventory. *Pain Practice*, *17,* 166-175. https://doi.org/10.1111/papr.12440

Neblett, R., Hartzell, M. M., Williams, M., Bevers, K. R., Mayer, T. G., Gatchel, R. J. (2017b). Use of the Central Sensitization Inventory (CSI) as a treatment outcome measure for patients with chronic spinal pain disorder in a functional restoration program. *The Spine Journal, 17,* 1819-1829. https://doi.org/10.1016/j.spinee.2017.06.008

Peduzzi, P., Concato, J., Feinstein, A.R., Holford, T.R. (1995). Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *Journal of Clinical Epidemiology*, *48*, 1503-1510.

Peduzzi, P., Concato, J., Kemper, E., Holford, T.R., Feinstein, A.R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology, 49,* 1373-1379.

Rabin, R., de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine, 33,* 337-343.

Scerbo, T., Colasurdo, J., Dunn, S., Unger, J., Nijs, J., Cook, C. (2018). Measurement properties of the central sensitization inventory: a systematic review. *Pain Practice*, *18,* 544-554.

Schulz, S., Brenk-Franz, K., Kratz, A., Petersen, J. J., Riedel-Heller, S. G., Schäfer, I.,…MultiCare Study Group. (2015). Self-efficacy in multimorbid elderly patients with osteoarthritis in primary care—influence on ain-related disability. *Clinical Rheumatology*, *34*, 1761-1767. https://doi.org/10.1007/s10067-014-2766-0

Sribney, W. (2003). A comparison of different tests for trend. https://www.stata.com/support/faqs/statistics/test-for-trend/

Stubhaug, A., Breivik, H., Eide, P. K., Kreunen, M., Foss, A. (1997). Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiologica Scandinavica, 41*, 1124-1132.

Tanaka, K., Nishigami, T., Mibu, A., Manfuku, M., Yono, S., Shinohara, Y.,…Ono, R. (2017). Validation of the Japanese version of the Central Sensitization Inventory in patients with musculoskeletal disorders. *PLoS One*, *12*, e0188719. https://doi.org/10.1371/journal.pone.0188719

Tsuchiya, A., Ikeda, S., Ikegami, N., Nishimura, S., Sakai, I., Fukuda, T.,…Tamura, M. (2002). Estimating an EQ-5D population value set: the case of Japan. *Health Economics*, *11*, 341-353. https://doi.org/10.1002/hec.673

Uki, J., Mendoza, T., Cleeland, C. S., Nakamura, Y., Takeda, F. (1998). A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory--BPI-J. *Journal of Pain and Symptom Management*, *16*, 364-373.

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, *152*, S2-15. https://doi.org/10.1016/j.pain.2010.09.030

Yunus, M. B. (2007). Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Practice & Research: Clinical Rheumatology, 21*, 481-497. https://doi.org/10.1016/j.berh.2007.03.006

van Wilgen, C. P., Konopka, K. H., Keizer, D., Zwerver, J., Dekker, R. (2013). Do patients with chronic patellar tendinopathy have an altered somatosensory profile? A Quantitative Sensory Testing (QST) study. *Scandinavian Journal of Medicine & Science in Sports*, *23*,

149-155. https://doi.org/10.1111/j.1600-0838.2011.01375.x

van der Noord, R., Paap, D., van Wilgen, C. P. (2018). Convergent validity and clinically relevant categories for the Dutch Central Sensitization Inventory in patients with chronic pain. *Journal of Applied Behavior Analysis Res*, e12119. https://doi.org/10.1111/jabr.12119