

# Cultural Validation of the Chinese Central Sensitization Inventory in Patients with Chronic Pain and its Predictive Ability of Comorbid Central Sensitivity Syndromes

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**Background:** Central sensitization (CS) is frequently reported in chronic pain, and the central sensitization inventory (CSI) is popularly used to assess CS. However, a validated Chinese CSI is lacking and its predictive ability for the comorbidity of central sensitivity syndromes (CSSs) remains unclear. Hence, this study aimed to generate the Chinese CSI (CSI-C) with cultural adaptation and examine its psychometric properties.

**Methods:** The CSI-C was formulated through forward and backward translation, panel review and piloting and then validated among patients with chronic pain ( $n = 235$ ). Its internal consistency, test-retest reliability, and concurrent validity were measured. An exploratory factor analysis (EFA) was performed for the construct validity. Receiver operating characteristic (ROC) analysis was employed to determine the discriminative ability in the presence of comorbidity of CSSs.

**Results:** About 70% of the participants in the study experienced at least mild CS symptoms. CSI-C demonstrates a high internal consistency (Cronbach's  $\alpha = 0.896$ ) and excellent test-retest reliability ( $ICC = 0.932$ ). CSI-C scoring was significantly correlated with pain intensity ( $r = 0.188$ ), EQ-5D index ( $r = -0.375$ ), anxiety ( $r = 0.525$ ), and depression ( $r = 0.467$ ). The EFA generated a 5-factor model, including physical symptoms, emotional distress, hypersensitivity syndromes and so on. An CSI cutoff of 42 had a sensitivity of 71.4% and a specificity of 70% for identifying chronic pain patients with  $\geq 2$  CSSs.

**Conclusion:** The CS manifestations are prevalent in those with persistent pain. CSI-C is a reliable and valid instrument for measuring CS. A CSI score  $\geq 42$  may predict the comorbidity of 2 or above CSSs in patients with chronic pain.

**Keywords:** central sensitization, chronic pain, central sensitization inventory, Chinese, central sensitivity syndrome

## Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".<sup>1</sup> Chronic pain refers to pain symptoms persisting for a prolonged duration of 3 months or above, which is a prevailing disorder affecting thousands of individuals across the world.<sup>1-5</sup> Increasingly high prevalence of chronic pain has been reported recently among the Chinese population, as high as 50% among the older people.<sup>3,4,6</sup>

Central sensitization (CS) is an exaggerated response in the central nervous system.<sup>5,7-9</sup> The principal signature of CS is pain hypersensitivity, including allodynia, punctate and/or pressure hyperalgesia,<sup>7-9</sup> and its pathophysiological mechanisms are probably related to maladaptive brain-orchestrated sensory processing.<sup>8,10-12</sup> CS was commonly found in those with chronic pain.<sup>5,8,10,13,14</sup> It may be partially accounted for the disproportionate pain manifestations

in persistent pain.<sup>12,15</sup> Worse still, the existence of CS in those with chronic pain is adversely correlated with pain remission and functional recovery, which thus tremendously influences their health-related quality of life (HR-QoL).<sup>5,8,15</sup> Given the refractory pain with CS, clinical health care providers are recommended to pinpoint the CS manifestation pattern in those with chronic pain,<sup>16,17</sup> and take into account both the peripheral and central elements of CS using a multifactorial model, employing “bottom-up” or “top-down” therapies to decrease peripheral nociception or weaken central pain sensitization.<sup>5</sup> However, current clinicians might tend to merely focus on the peripheral mechanism and a multifaceted pain management perspective may not be adequately considered.<sup>5</sup>

Central sensitivity syndromes (CSSs) are a group of various kinds of disorders with common symptomatology of ongoing pain and hypersensitivity.<sup>18–20</sup> The commonplace CSSs include fibromyalgia (FM), irritable bowel syndrome (IBS), chronic headache or migraine, temporomandibular joint disorders (TMDs), pelvic pain syndromes, chronic fatigue syndrome, multiple chemical sensitivities, and restless leg syndrome.<sup>18,19,21,22</sup> CSSs are related to widespread pain beyond one specific area and may also be accompanied by other complaints such as fatigue, sleep disturbances, as well as difficulties in concentration.<sup>18</sup> The exact pathophysiological mechanisms of CSSs remain not well understood, especially across various CSSs.<sup>22–25</sup> CS is perceived as the common indicator that bridges over different CSSs with overlapping clinical manifestations.<sup>22,23</sup> The hypersensitivity syndromes have placed an adverse impact on their pain complaint and daily function, as well as on the interaction with healthcare providers.<sup>26</sup>

The assessment and diagnosis of CS mainly rely on quantitative sensory testing (QST).<sup>12,27</sup> Despite its advantages in standardized and quantitative measurements of CS, QST requires relatively expensive apparatuses and is time and labor-consuming, which limits its widespread use.<sup>8,12</sup> Another indirect measure scale specifically designed for CS, the Central Sensitization Inventory (CSI) has been adopted to assess CS symptoms.<sup>8,10,28</sup> The CSI scale has two parts, namely: Part A and Part B. Part A is comprised of 25 health-related questions focusing on physical symptoms, mental distress, headache and jaw disorders, as well as urological and bowel discomfort.<sup>12,28</sup> For each item, 5 levels of the Likert scale including “never”, “rarely”, “sometimes”, “often”, and “always” are provided for scoring. Part B (without scoring) aims to find out if the participants have been diagnosed with a list of disorders including CSSs and anxiety and depression. In addition, the clinically relevant severity levels for CSI were established, which included 5 categories, namely subclinical CS (0–29), mild (30–39), moderate (40–49), severe (50–59), and extreme CS ( $\geq 60$ ).<sup>29</sup>

The psychometric properties of the CSI in English, as well as other languages, have been evaluated and shown to be a solid instrument to screen CS symptoms.<sup>10,30–33</sup> However, a valid Chinese version of CSI is still lacking. Moreover, the predictive power of CSI for identifying the comorbidity of CSSs among those with chronic pain remains not well understood. Therefore, this study would like to generate an appropriate Chinese version of CSI and validate it in Chinese population with chronic pain. Specifically, the psychometric properties including internal consistency, test–retest reliability, concurrent validity, construct validity, and discriminative ability to identify CSS comorbidity were investigated.

## Materials and Methods

### Translation and Cultural Adaptation of the CSI

The procedures of translation and cross-cultural adaptation of CSI were implemented in accord with the international guidelines.<sup>34</sup> Firstly, forward translation was conducted to translate the original English CSI into Chinese. Then, the variations between the two aforementioned translated versions were discussed and resolved with an extra bilingual translator. The second step was backward translation. Afterwards, an expert committee consisting of two experts who were familiar with the construct of the CSI scale, a professor in biostatistics, and forward and backward translators were established to review all versions of the translations and come out with a consensus for the prefinal version of the Chinese CSI. Pilot testing was conducted among a small sample of 30 participants with chronic pain. Lastly, a finalized Chinese version of the CSI (CSI-C) was generated.

### Participants

Participants with chronic pain were consecutively enrolled from two public hospitals in Hong Kong between May 2020 and May 2021. The inclusion criteria included: a) aged 18 years or above; b) experiencing musculoskeletal pain symptoms with

a duration of no less than 3 months; c) having competency in the Chinese language comprehension and to complete the scales used in the study. The exclusion criteria were as follows: a) abnormal mental or cognitive status; b) diagnosis of certain medical conditions that influence the central nervous system, including cancer, brain or spinal cord injury, neurological disease or injuries; c) other reasons leading to a failure to comply with the experimental protocols. Among the participants, a subset of patients ( $n = 64$ ) was asked to complete the CSI-C again within an interval of 3 weeks.

All participants were informed about the purpose of the study and asked to give written consent before joining the study. The present study was conducted in accordance with the Helsinki Declaration and approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref. No. 20–294).

## Sample Size Estimate

The sample size for this study was calculated based on previous validation studies in other languages.<sup>30,31,35</sup> According to the theoretical method used in relevant validation study and factor analysis, a respondent-to-item ratio of no less than 5:1 is adopted.<sup>36</sup> Given that the CSI has 25 items for questioning, at least 125 participants with chronic pain should be included. We believe the current sample size of 235 is capable of maintaining sufficient power for this study.

## Statistical Analysis

The Shapiro–Wilk’s test was employed to test the normality distribution of the variables in the study, with the inspection of histograms, normal Q-Q plots and box plots as well. The internal consistency of the CSI-C was examined using Cronbach’s alpha. Intra-class correlation coefficient (ICC) was calculated to testify the test–retest reliability of CSI-C.

An exploratory factor analysis (EFA) was employed for data reduction and the construct validity of the scale. Since the 25-item CSI scale is set to collect response by categorical responses, the EFA is performed using the unweighted least square for extraction, which has been validated by previous studies on research methods for factor analysis on ordinal data.<sup>37,38</sup> Besides, considering the possible inter-factor correlation, an oblique rotation method was adopted via Promax with Kaiser Normalization. The significance threshold for factor loading was set at 0.40.

The concurrent validity is usually conducted by comparing the target tool with other relevant health-related patient reported outcome measures such as quality of life.<sup>10</sup> In the present study, CSI-C mainly looks at pain sensitization, which is often associated with negative emotions as anxiety and depression.<sup>39</sup> Hence, the concurrent validity of CSI-C was investigated by the correlations between CSI-C score and the pain intensity, health-related quality of life (EuroQol-5D (EQ-5D) index),<sup>40</sup> anxiety and depression (hospital anxiety and depression scale (HADS)).<sup>41</sup> The variable of total CSI score follows a Gaussian distribution, while other variables including EQ-5D index, anxiety and depression score, as well as pain intensity were not normally distributed. Therefore, Spearman correlations were conducted for the above-mentioned correlational analyses. The strength of the correlation was measured by the correlation coefficient, above 0.5, 0.35 to 0.5, and lower than 0.35 indicated strong, moderate, and weak correlations, respectively.<sup>42</sup>

The discriminative ability to identify CSS comorbidity in chronic pain was determined by the receiver operating characteristic (ROC) curve. Area under the curve (AUC) of ROC analysis was adopted to establish the optimal cut-off CSI score for identifying patients with chronic pain with 2 or more CSSs comorbidity. The statistical analyses were performed using version 27.0 of the IBM® SPSS® Statistics software (IBM Corp.; NY; USA). The significance level in the study was set at 0.05.

## Results

### Characteristics of Participants Included

A total of 235 participants with chronic pain were recruited for the study. The majority of patients were female, with an average age of over 60 years. In terms of the pain feature, patients with chronic musculoskeletal pain recruited in the study were further classified into categories of “nociceptive”, “neuropathic”, and “mixed of nociceptive and neuropathic”, depending on the clinical indicators by the existing evidence of the mechanisms-based classifications of musculoskeletal pain.<sup>16,43</sup>

The demographic and clinical characteristics of the participants are presented in [Table 1](#).

**Table I** Participant Characteristics

		Value
Sex, n (%)	Male	39 (16.60)
	Female	196 (83.40)
Age (years)	Mean (SD)	64.2(9.53)
BMI	Mean (SD)	24.2(4.08)
Employment, n (%)	Employed	68 (28.94)
	Unemployed	79(33.62)
	Retired	82(34.89)
	Others	6 (2.55)
Musculoskeletal pain classification	-Neuropathic	72(30.60)
	-Nociceptive	132(56.20)
	-Mixed	31(13.20)
Duration of pain (years)	Mean (SD)	4.2(5.04)
CSI total score	Mean (SD)	36.4(13.10)
Average pain intensity	Mean (SD)	5.7(1.50)
Maximal pain intensity	Mean (SD)	7.3(1.67)
EQ-5D index	Mean (SD)	0.6(0.15)
Anxiety score	Mean (SD)	6.3(3.66)
Depression score	Mean (SD)	6.4(3.91)

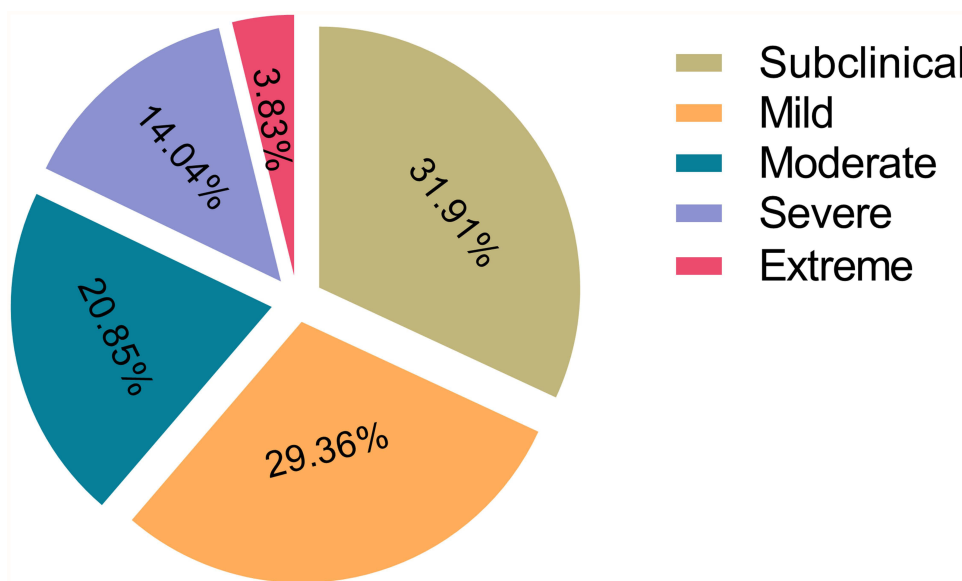
**Abbreviations:** BMI, body mass index; CSI, central sensitization inventory; EQ-5D, EuroQol-5D; SD, standard deviation.

### CS Severity

Approximately 70% (160/235) of the participants experienced at least mild clinical CS symptoms in the present study with CSI-C scores of 30 or above. About 40% of the participants were presented with moderate- or above-level CS. [Figure 1](#) shows the distribution of the participants with varied severity levels of CS.

### Internal Consistency and Test–Retest Reliability

The internal consistency of the CSI-C was high with the Cronbach’s alpha of 0.896. In addition, of the participants included, 64 completed the CSI-C questionnaire twice within an interval of 3 weeks. An excellent test–retest reliability was found in the study (ICC = 0.932).



**Figure 1** Distribution of severity levels of central sensitization.

**Table 2** Correlations Between CSI and Clinical Symptoms

Variable	Correlation Coefficient	p value
Duration of pain	-0.074	0.258
Pain intensity	0.188	0.004
EQ-5D index	-0.375	<0.001
Anxiety	0.525	<0.001
Depression	0.467	<0.001

**Abbreviations:** CSI, central sensitization inventory; EQ-5D, EuroQol-5D.

## Concurrent Validity

The concurrent validity of CSI-C was evaluated by correlating CSI-C scoring with clinical parameters such as pain intensity, HR-QoL, and anxiety and depression scores. As seen in Table 2, CSI-C scoring was significantly correlated with pain intensity, EQ-5D index, anxiety and depression. No statistically significant correlation was found between the duration of pain and CSI-C scores.

## Construct Validity

The EFA generated a 5-factor model, including factors on “physical symptoms”, “emotional distress”, “hypersensitivity syndrome”, “concentration and memory problem”, as well as “bladder & teeth grinding disorders”, which explained 51.6% of the total variances (see Table 3).

**Table 3** Factor Loading of the Exploratory Factor Analysis

Item Number	Item Topic	F1	F2	F3	F4	F5	Not Loading
1	Unrefreshed in the morning	0.270	0.179	0.277	0.090	-0.048	X
2	Muscle stiff/achy	<b>0.624</b>	-0.176	0.180	-0.077	0.033	
3	Anxiety attacks	0.121	-0.077	<b>0.766</b>	-0.075	0.066	
4	Grind/clench teeth	0.070	-0.059	-0.016	<b>0.457</b>	0.178	
5	Diarrhea/constipation	0.014	0.055	0.086	0.150	0.193	X
6	Need help with daily activities	0.222	0.277	0.096	0.022	0.099	X
7	Sensitive to bright lights	0.249	0.133	-0.182	0.056	<b>0.593</b>	
8	Easily tired with physical activity	<b>0.444</b>	0.339	0.061	-0.117	0.038	
9	Pain all over body	<b>0.781</b>	-0.005	-0.113	0.276	-0.163	
10	Headaches	0.280	0.042	0.336	0.048	-0.010	X
11	Bladder/urination pain	-0.083	-0.091	0.183	<b>0.543</b>	0.220	
12	Do not sleep well	0.054	0.393	0.309	-0.138	0.016	X
13	Difficulty concentrating	-0.293	<b>0.780</b>	0.102	0.094	0.096	
14	Skin problems	-0.072	0.111	-0.020	0.322	0.131	X
15	Stress makes symptoms worse	0.066	0.140	0.384	0.260	-0.063	X
16	Sad or depressed	-0.055	0.152	<b>0.802</b>	0.010	-0.113	
17	Low energy	0.281	<b>0.706</b>	-0.046	-0.022	-0.047	
18	Tension in neck and shoulder	<b>0.651</b>	-0.006	0.017	-0.186	0.269	
19	Pain in jaw	0.124	-0.200	0.145	0.251	0.284	X
20	Certain smells make dizzy	0.031	0.168	0.069	0.247	0.110	X
21	Urinate frequently	-0.149	0.184	0.027	0.010	<b>0.484</b>	
22	Restless legs	0.211	0.230	0.086	0.088	0.004	X
23	Poor memory	-0.038	<b>0.495</b>	-0.121	0.137	0.199	
24	Trauma as a child	-0.047	0.145	-0.075	<b>0.556</b>	-0.069	
25	Pelvic pain	0.329	-0.002	-0.103	0.366	-0.142	X

**Notes:** The values in bold indicate the item meets the requirement for factor loading (significance threshold of 0.40). X means the item is not loading.

**Table 4** Diagnoses of Central Sensitivity Syndromes

	Number (%)
<b>Diagnoses</b>	
Restless leg syndrome	0
Chronic fatigue syndrome	2 (0.85)
Fibromyalgia	3 (1.28)
Temporomandibular joint disorder	1 (0.43)
Migraine or tension headache	18 (7.66)
Irritable bowel syndrome	16 (6.81)
Multiple chemical sensitivities	0
Neck injury (including whiplash)	5 (2.13)
Anxiety or panic attack	20 (8.51)
Depression	44 (18.72)

Factor 1 focused on physical symptoms, including four items (items 2, 8, 9, 18). Factor 2 was pertaining to concentration and memory problem, encompassing 3 items (items 13, 17, 23). Factor 3 was on emotional distress, involving 2 items on anxiety and depression (items 3 and 16). Factor 4 was mainly related to teeth grinding and urination pain with 3 items (items 4, 11, 24). Factor 5 was about hypersensitivity presentations including 2 items (items 7 and 21). There were ten items not loading on the factor analysis, including items 1, 5, 6, 10, 12, 14, 15, 19, 20, 22, and 25. Also, correlations were found in the inter-factor correlation matrix ([Supplementary Table S1](#)).

## CSSs

There were 7 separate CSSs in part B of CSI-C ([Table 4](#)). Of all participants in this study, 31 were diagnosed previously with at least one CSS. Around 10% (24/235) had one single CSS, and 3% (7/235) presented with 2 or more CSSs ([Table 5](#)). The most common CSS found in the study was migraine or tension headache, followed by IBS. Besides CSSs, a small number of participants had diagnoses of anxiety or panic attacks and/or depression. The CSI scores in those with 2 or above CSSs were significantly higher, compared with those without CSS (48.3 vs 35.5,  $p=0.032$ ).

## AUC-ROC Analysis

[Figure 2](#) demonstrates the AUC-ROC curve revealing the predictive ability of CSI-C in identifying patients with two or more CSSs. The AUC was 0.737, with 95% CI values of 0.565 and 0.908. The CSI cutoff score of 42 was able to predict the presence of 2 or above CSSs in those with persistent pain, with a sensitivity of 71.4% and a specificity of 70%.

## Discussion

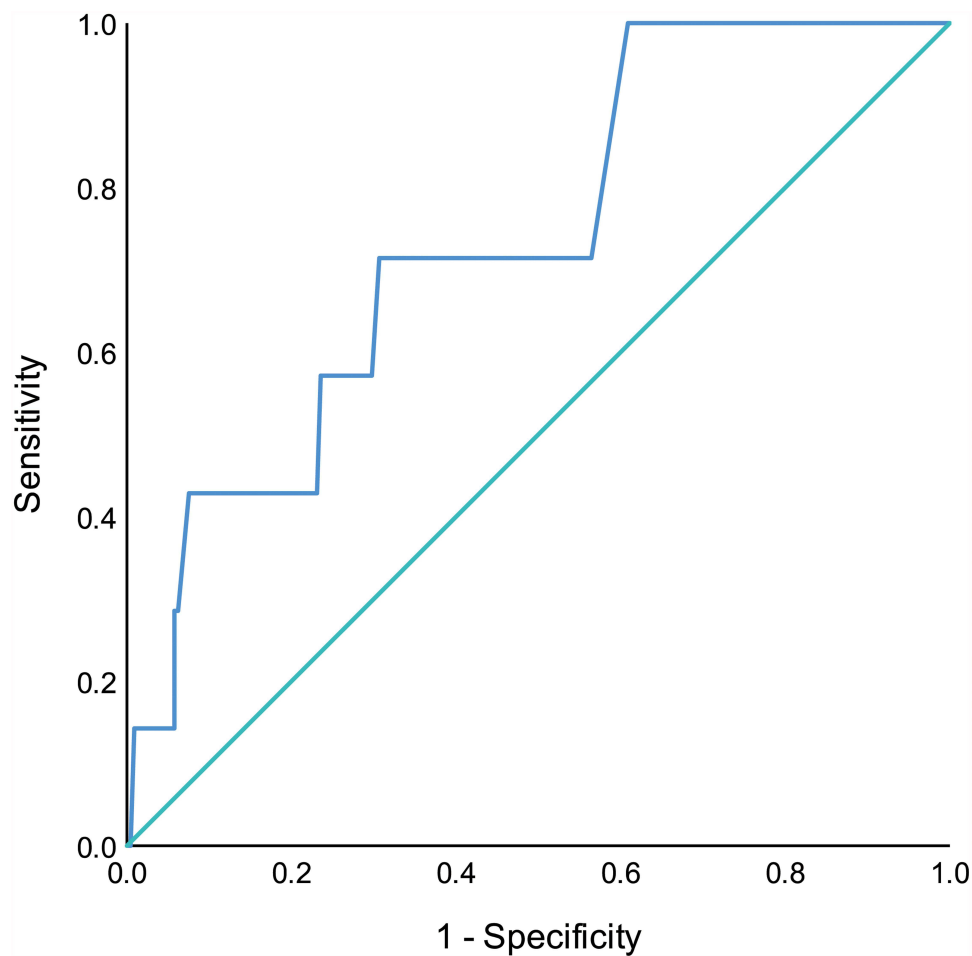
As noted, this is the first study to validate the Chinese version of CSI with cultural adaptation among chronic pain patients and investigate the discriminative ability of CSI scoring in identifying those with the comorbidity of CSSs. Our findings demonstrate that CSI-C has excellent test–retest reliability and high internal consistency. The 5-factor structured

**Table 5** CSI-C Scores Between Participants with and without Central Sensitivity Syndrome

Category	CSI-C Total Score Mean (SD)	95% CI
No CSS (n=204)	35.5 (12.93) *	(33.74–37.31)
1 CSS (n=24)	40.7 (12.51)	(35.39–45.95)
2 and above CSSs (n=7)	48.3 (13.33) *	(35.96–60.61)

**Note:** \*Represents significant difference between “No CSS” group and “2 and above CSSs” group.

**Abbreviations:** CSS, central sensitivity syndrome; CSI-C, Chinese version of central sensitization inventory; SD, standard deviation; CI, confidence interval.



**Figure 2** Receiver operating characteristic curve.

CSI-C driven by factor analysis was significantly correlated with pain-related health outcomes. CSI score higher or equal to 42 may adequately predict the comorbid CSSs (2 or more) in patients with chronic pain.

The presence of CS has previously been evidenced in persistent pain disorders including chronic headache, musculoskeletal pain, as well as neuropathic pain.<sup>44–49</sup> CS can be measured by quantitative methods for heat and cold pain thresholds as well as pressure pain thresholds.<sup>12,27,50</sup> Given the time- and labor-consuming nature of QST measures, a CSI scale has been developed to screen CS in clinical practice.<sup>10,28</sup> Of the 235 patients with chronic pain in the present study, about 70% were presented with clinical CS (score higher than 29), and approximately 40% developed moderate or severe, or even extreme CS. The prevalence of CS found in our study is in line with previous findings about chronic migraine or low back pain.<sup>44,46,51</sup> However, it is much higher than that in a Japanese study on chronic musculoskeletal pain (less than 30%).<sup>31</sup> The discrepancies could be explained by the different clinical characteristics of the sample population in the present study. As seen, our samples are comprised of a majority of older female individuals with pain symptoms lasting for years. The distinct pain profiles as well as the relatively high pain intensity of the patient cohort may also contribute to the prevalence of CS presentation in this work.

Regarding the reliability of CSI-C, good internal consistency and excellent test–retest reliability were found. The Cronbach’s alpha of CSI-C was 0.896, which was similar to the original English version of CSI (Cronbach’s alpha = 0.87),<sup>10,28</sup> as well as other translated versions including Dutch, Spanish, and Japanese.<sup>30,33,35,52</sup> Moreover, the ICC for test–retest reliability in the study was 0.932, compared with previous reports on CSI in different languages with ICCs ranging from 0.817 to 0.971.<sup>10,28,30,33,35,52</sup>

In terms of the concurrent validity, a significant negative correlation was discovered between CSI-C and EQ-5D index measuring HR-QoL ( $r = -0.375$ ). Furthermore, CSI-C was positively associated with pain intensity, as well as anxiety and depression ( $r = 0.188$ ,  $r = 0.525$ ,  $r = 0.467$ , respectively). The criterion validity of CSI-C is consistent with previous studies.<sup>35,49,53,54</sup> Of note, a strong or moderate to strong correlation was found between CSI-C and anxiety or depression in our study. Similarly, previous research revealed that chronic pain patients with CS were associated with elevated scores on depression scales.<sup>39</sup> In the study, 20 participants had a diagnosis of anxiety or panic attack and 44 had depression. As anxiety or depression is also a common comorbidity of refractory pain,<sup>55,56</sup> it would be worthwhile for further research to undertake in-depth investigations towards the interplay between anxiety and/or depression and pain sensitization.

As for the dimensionality of CSI-C, the factor analysis yielded a 5-factor model (Table 3), which was, to some extent, slightly different from the English version as well as other language versions.<sup>10,28,30,31</sup> In the original English version of CSI, four domains were formulated, namely “physical symptoms”, “emotional distress”, “headache/jaw symptoms”, and “urological symptoms”,<sup>28</sup> whereas in the Dutch version, the four-factor model was of some variations, including a new factor of “higher central sensitivity” besides the physical and emotional disorders as well as the urological and skin problems.<sup>30</sup> In the present study, the 5 factors explained 51.57% of the total variances. Three factors concerning “physical symptoms”, “emotional distress”, and “hypersensitivity syndrome” were in line with the previous studies.<sup>28,30</sup> Nevertheless, three additional factors involving “concentration and memory problem”, “teeth and bladder disorders” were identified. The discrepancies in dimensions found in factor analysis across studies may be related to the variations in different language versions of CSI.<sup>10</sup> Besides, the sample population with varied pain features between our study and the others could also contribute to the differences in construct validity analysis.<sup>10</sup>

CSSs are challenging disorders with refractory pain complaints and abnormal pain sensitization.<sup>18</sup> Seven separate CSSs were included in part B of CSI-C, namely restless leg syndrome, chronic fatigue syndrome, FM, TMDs, migraine or tension headache, IBS, and multiple chemical sensitivities. The co-existence of CSSs with chronic pain disorders has undoubtedly complicated the story of pain experience and CS.<sup>57</sup> Thirty-one patients in the study were diagnosed with at least one CSS. According to previous studies, a cut-off score of 40 out of 100 in CSI is appropriate for differentiating patients with CSSs and the healthy controls.<sup>31,52</sup> In our study, 40% (91/235) of the participants were manifested with moderate or above CS with CSI score larger or equal to 40. About 13% of participants with chronic pain in the study reported having one or more CSSs. Participants with two or more CSSs scored significantly higher than those without CSS. The AUC-ROC analysis in the study demonstrated an AUC of 0.737 (95% CI: 0.565–0.908). We found that a CSI cutoff score of 42 may adequately discriminate between those patients with two or above CSSs in the outpatient chronic pain sample, with a sensitivity of 71.4% and specificity of 70%, respectively. Considering the complexity of etiology for CSS, future studies are thus warranted to explore the influence of CSSs on pain exacerbation and CS.<sup>52</sup>

There existed both strengths and limitations in the present study. Our study firstly attempted to translate the CSI into CSI-C with cultural adaptation and perform a thorough validation of it. A relatively large sample of participants with chronic pain from two outpatient clinics in public hospitals in Hong Kong was included. Priori estimate of the study sample size was conducted to ensure sufficient statistical power. What is more, considering the pain intensity and duration, our participants represented a painful sample population with medium-to-high pain severity and chronicity, who tended to be more vulnerable to developing CS symptoms, and thus more responsive to CSI-C. Given the excellent reliability, internal consistency, and recognized validity, CSI-C is recommended to be used by first-line clinicians. Since CSI-C is a self-administered outcome measure, it facilitates an easy implementation in the clinical settings. The validated CSI-C is available from the corresponding author on reasonable request. Besides the evaluation of several crucial validities, the present study investigated the discriminative ability of CSI in identifying the comorbidity of CSSs among patients with persistent pain. The CSI cutoff score of 42 was found to adequately predict those having 2 or more CSSs in this study.

As for the limitations, first, the vast majority of the samples were female and older adults, which could place a limit on the generalizability of the results. Also, the mixed pain feature with neuropathic and nociceptive components in the sample population may affect the dimensions in factor analysis in our study, compared with previous ones. The lack of normal control limits the analysis of discriminative power differentiating chronic pain patients and the non-patient

control. Another limitation is that QST was not included in the study to measure CS objectively. Among those with chronic pain such as fibromyalgia and osteoarthritis, aberrant sensory profiles by QST have been demonstrated by previous evidence.<sup>58,59</sup> Hence, future studies are warranted to correlate the CSI scoring with QST measurements. Since it is a cross-sectional study without longitudinal follow-up analyses, the sensitivity and responsiveness of CSI-C cannot be assessed. In terms of the self-reported CSS in part B of the CSI-C, there might exist a response bias.

## Conclusion

In conclusion, CS manifestations are prevalent in those with persistent pain. Our findings reveal that CSI-C is a solid tool in the measurement of CS symptoms in Chinese patients with chronic pain with excellent reliability and recognized validities. A CSI score  $\geq 42$  may be of value in identifying chronic pain patients with two or above comorbid CSSs. The prevalent CS manifestations and comorbidities of CSSs in chronic pain deserve further research in the future so as to optimize pain management.

## Abbreviations

AUC, area under the curve; CS, central sensitization; CSI, central sensitization inventory; CSI-C, Chinese version of central sensitization inventory; CSS, central sensitivity syndrome; EFA, exploratory factor analysis; EQ-5D, EuroQoL-5D; FM, fibromyalgia; HR-QoL, health-related quality of life; HADS, hospital anxiety and depression scale; ICC, intraclass correlation coefficient; IBS, irritable bowel syndrome; QST, quantitative sensory testing; ROC, receiver operating characteristic; TMD, temporomandibular joint disorder.

## Data Sharing Statement

The datasets used and analyzed during the current study as well as the validated CSI-C scale are available from the corresponding author (Wing-Yuk Ip, wyip@hku.hk) on reasonable request for academic purpose.

## Acknowledgments

The authors would like to thank all the participants in the study.

## Author Contributions

All authors made a significant contribution to the current manuscript, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by the Guangdong Hopson-Pearl River Education Development Foundation (No. H20190116202012724) and National Natural Science Foundation of China (No. 81472155). The funders above were not involved in any research aspects, such as study design, data collection and analysis, report writing and paper submission.

## Disclosure

All authors declare no conflicts of interest in this work.

## References

1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–1982. doi:10.1097/j.pain.0000000000001939
2. Pitcher MH, Von Korff M, Bushnell MC, Porter L. Prevalence and profile of high-impact chronic pain in the United States. *J Pain*. 2019;20(2):146–160. doi:10.1016/j.jpain.2018.07.006
3. Li J, Chen J, Qin Q, et al. Chronic pain and its association with obesity among older adults in China. *Arch Gerontol Geriatr*. 2018;76:12–18. doi:10.1016/j.archger.2018.01.009

4. Si H, Wang C, Jin Y, et al. Prevalence, factors, and health impacts of chronic pain among community-dwelling older adults in China. *Pain Manag Nurs.* 2019;20(4):365–372. doi:10.1016/j.pmn.2019.01.006
5. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision Medicine. *Lancet Rheumatol.* 2021;3(5):E383–E392. doi:10.1016/S2665-9913(21)00032-1
6. Xiao H, Liu H, Liu J, et al. Pain prevalence and pain management in a Chinese hospital. *Med Sci Monit.* 2018;24:7809–7819. doi:10.12659/MSM.912273
7. Gatchel RJ, Neblett R. Central sensitization: a brief overview. *J Appl Biobehav Res.* 2018;23(2):e12138. doi:10.1111/jabr.12138
8. Nijs J, Polli A, Malfliet A, Huysmans E, Coppieters I. Central sensitisation: another label or useful diagnosis? *Drug Ther Bull.* 2019;57(4):60. doi:10.1136/dtb.2018.000035
9. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature.* 1983;306(5944):686–688. doi:10.1038/306686a0
10. Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement properties of the Central Sensitization Inventory: a systematic review. *Pain Pract.* 2018;18(4):544–554. doi:10.1111/papr.12636
11. Alomar S, Bakhaidar M. Neuroimaging of neuropathic pain: review of current status and future directions. *Neurosurg Rev.* 2018;41(3):771–777. doi:10.1007/s10143-016-0807-7
12. Akinci A, Al Shaker M, Chang MH, et al. Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component. *Int J Clin Pract.* 2016;70(1):31–44. doi:10.1111/ijcp.12749
13. Gervais-Hupé J, Pollice J, Sadi J, Carlesso L. Validity of the central sensitization inventory with measures of sensitization in people with knee osteoarthritis. *Clin Rheumatol.* 2018;37(11):3125–3132. doi:10.1007/s10067-018-4279-8
14. Lluch E, Nijs J, Courtney CA, et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. *Disabil Rehabil.* 2018;40(23):2836–2845. doi:10.1080/09638288.2017.1358770
15. Guler MA, Celik OF, Ayhan FF. The important role of central sensitization in chronic musculoskeletal pain seen in different rheumatic diseases. *Clin Rheumatol.* 2019;39(1):269–274. doi:10.1007/s10067-019-04749-1
16. Nijs J, Apeldoorn A, Hallegraef H, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician.* 2015;18(3):E333–E345. doi:10.36076/ppj.2015/18/E333
17. Nijs J, Torres-Cueco R, Van wilgen P, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician.* 2014;17(5):447–457. doi:10.36076/ppj.2014/17/447
18. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. *Curr Rheumatol Rev.* 2015;11(2):96–108. doi:10.2174/1573397111666150619095330
19. Neblett MR, Hartzell GM, Cohen JH, et al. Ability of the Central Sensitization Inventory to identify central sensitivity syndromes in an outpatient chronic pain sample. *Clin J Pain.* 2015;31(4):323–332. doi:10.1097/AJP.0000000000000113
20. Jones GT. Psychosocial vulnerability and early life adversity as risk factors for central sensitivity syndromes. *Curr Rheumatol Rev.* 2016;12(2):140–153. doi:10.2174/1573397112666151231113438
21. Haruyama Y, Sairenchi T, Uchiyama K, Suzuki K, Hirata K, Kobashi G. A large-scale population-based epidemiological study on the prevalence of central sensitization syndromes in Japan. *Sci Rep.* 2021;11(1):23299. doi:10.1038/s41598-021-02678-1
22. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum.* 2007;36(6):339–356. doi:10.1016/j.semarthrit.2006.12.009
23. Walitt B, Ceko M, Gracely JL, Gracely RH. Neuroimaging of central sensitivity syndromes: key insights from the scientific literature. *Curr Rheumatol Rev.* 2016;12(1):55–87. doi:10.2174/1573397112666151231111104
24. Martínez-Martínez LA, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. *J Clin Rheumatol.* 2014;20(3):146–150. doi:10.1097/RHU.0000000000000089
25. Maugars Y, Berthelot JM, Le Goff B, Darrieutort-Laffite C. Fibromyalgia and associated disorders: from pain to chronic suffering, from subjective hypersensitivity to hypersensitivity syndrome. *Front Med.* 2021;8:666914. doi:10.3389/fmed.2021.666914
26. Wang XJ, Ebbert JO, Gilman EA, Rosedahl JK, Ramar P, Philpot LM. Central sensitization symptom severity and patient-provider relationships in a community setting. *J Prim Care Community Health.* 2021;12:21501327211031767. doi:10.1177/21501327211031767
27. 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(10):1367–1375. doi:10.1002/j.1532-2149.2014.499.x
28. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract.* 2012;12(4):276–285. doi:10.1111/j.1533-2500.2011.00493.x
29. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing clinically relevant severity levels for the Central Sensitization Inventory. *Pain Pract.* 2017;17(2):166–175. doi:10.1111/papr.12440
30. Kregel JJ, Vuijk JP, Descheemaeker JF, et al. The Dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. *Clin J Pain.* 2016;32(7):624–630. doi:10.1097/AJP.0000000000000306
31. Tanaka K, Nishigami T, Mibu A, et al. Validation of the Japanese version of the Central Sensitization Inventory in patients with musculoskeletal disorders. *PLoS One.* 2017;12(12):e0188719. doi:10.1371/journal.pone.0188719
32. Knezevic A, Neblett R, Jeremic-Knezevic M, et al. Cross-cultural adaptation and psychometric validation of the Serbian version of the central sensitization inventory. *Pain Pract.* 2018;18(4):463–472. doi:10.1111/papr.12618
33. Cuesta-Vargas AI, Neblett R, Chiarotto A, et al. Dimensionality and reliability of the central sensitization inventory in a pooled multicountry sample. *J Pain.* 2018;19(3):317–329. doi:10.1016/j.jpain.2017.11.006
34. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol.* 1993;46(12):1417–1432. doi:10.1016/0895-4356(93)90142-N
35. Cuesta-Vargas A. Cross-cultural adaptation and validity of the Spanish central sensitization inventory. *Springerplus.* 2016;5(1):1837. doi:10.1186/s40064-016-3515-4
36. Anthoine E, Moret L, Regnault A, Sébille V, Hardouin J-B. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. *Health Qual Life Outcomes.* 2014;12:176. doi:10.1186/s12955-014-0176-2

37. Morata-Ramírez M, Holgado-Tello FP. Construct validity of Likert scales through confirmatory factor analysis: a simulation study comparing different methods of estimation based on Pearson and polychoric correlations. *Int J Soc Sci Stud.* 2013;1:54.
38. Li C-H. Confirmatory factor analysis with ordinal data: comparing robust maximum likelihood and diagonally weighted least squares. *Behav Res Methods.* 2016;48(3):936–949. doi:10.3758/s13428-015-0619-7
39. López-Ruiz M, Losilla JM, Monfort J, et al. Central sensitization in knee osteoarthritis and fibromyalgia: beyond depression and anxiety. *PLoS One.* 2019;14(12):e0225836. doi:10.1371/journal.pone.0225836
40. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727–1736. doi:10.1007/s11136-011-9903-x
41. Wang W, Chair SY, Thompson DR, Twinn SF. A psychometric evaluation of the Chinese version of the Hospital Anxiety and Depression Scale in patients with coronary heart disease. *J Clin Nurs.* 2009;18(13):1908–1915. doi:10.1111/j.1365-2702.2008.02736.x
42. Lin K, Bao L, Wang J, Fujita K, Makimoto K, Liao X. Validation of the Chinese (Mandarin) version of the Oxford knee score in patients with knee osteoarthritis. *Clin Orthop Relat Res.* 2017;475(12):2992–3004. doi:10.1007/s11999-017-5495-2
43. Smart KM, Blake C, Staines A, Doody C. The Discriminative validity of “nociceptive,” “peripheral neuropathic,” and “central sensitization” as mechanisms-based classifications of musculoskeletal pain. *Clin J Pain.* 2011;27(8):655–663. doi:10.1097/AJP.0b013e318215f16a
44. de Tommaso M, Scirucchio V, Delussi M, et al. Symptoms of central sensitization and comorbidity for juvenile fibromyalgia in childhood migraine: an observational study in a tertiary headache center. *J Headache Pain.* 2017;18(1):59. doi:10.1186/s10194-017-0764-8
45. Filatova E, Latysheva N, Kurenkov A. Evidence of persistent central sensitization in chronic headaches: a multi-method study. *J Headache Pain.* 2008;9(5):295–300. doi:10.1007/s10194-008-0061-7
46. Suzuki K, Suzuki S, Shiina T, et al. Investigating the relationships between the burden of multiple sensory hypersensitivity symptoms and headache-related disability in patients with migraine. *J Headache Pain.* 2021;22(1):77. doi:10.1186/s10194-021-01294-8
47. Terry EL, Booker SQ, Cardoso JS, et al. Neuropathic-like pain symptoms in a community-dwelling sample with or at risk for knee osteoarthritis. *Pain Med.* 2020;21(1):125–137. doi:10.1093/pm/pnz112
48. O’leary MH, Smart AK, Moloney MN, Blake MC, Doody MC. Pain sensitization associated with nonresponse after physiotherapy in people with knee osteoarthritis. *Pain.* 2018;159(9):1877–1886. doi:10.1097/j.pain.0000000000001288
49. Roh HY, Koh DY, Kim OJ, Lee HK, Gong SH, Baek HG. Preoperative pain sensitization is associated with postoperative pillar pain after open carpal tunnel release. *Clin Orthop Relat Res.* 2018;476(4):734–740. doi:10.1007/s11999-000000000000096
50. Gírbés E, Nijs J, Torres-Cueco R, Cubas C. Pain treatment for patients with osteoarthritis and central sensitization. *Phys Ther.* 2013;93(6):842–851. doi:10.2522/ptj.20120253
51. Aoyagi K, He J, Nicol AL, et al. A subgroup of chronic low back pain patients with central sensitization. *Clin J Pain.* 2019;35(11):869–879. doi:10.1097/AJP.0000000000000755
52. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain.* 2013;14(5):438–445. doi:10.1016/j.jpain.2012.11.012
53. Wilgen CP, Vuijk PJ, Kregel J, et al. Psychological distress and widespread pain contribute to the variance of the central sensitization inventory: a cross-sectional study in patients with chronic pain. *Pain Pract.* 2018;18(2):239–246. doi:10.1111/papr.12600
54. Lluich gírbés E, Dueñas L, Barbero M, et al. Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis. *Phys Ther.* 2016;96(8):1196–1207. doi:10.2522/ptj.20150492
55. Doan L, Manders T, Wang J. Neuroplasticity underlying the comorbidity of pain and depression. *Neural Plast.* 2015;2015:504691. doi:10.1155/2015/504691
56. McCallum LM, Damms NA, Sarrigiannis PG, Zis P. Anxiety and depression in patients with suspected carpal tunnel syndrome – a case controlled study. *Brain Behav.* 2019;9(7):e01342. doi:10.1002/brb3.1342
57. Suzuki K, Haruyama Y, Kobashi G, et al. Central sensitization in neurological, psychiatric, and pain disorders: a multicenter case-controlled study. *Pain Res Manag.* 2021;2021:6656917. doi:10.1155/2021/6656917
58. Davis KD. Imaging vs quantitative sensory testing to predict chronic pain treatment outcomes. *Pain.* 2019;160(Suppl 1):S59–S65. doi:10.1097/j.pain.0000000000001479
59. Smith SM, Dworkin RH, Turk DC, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *J Pain.* 2017;18(7):757–777. doi:10.1016/j.jpain.2017.02.429