INTRODUCTION

Patients with fibromyalgia (FM) complain many symptoms besides musculoskeletal pain: for example, fatigue, sleep difficulties, a swollen feeling in tissues, paresthesia, cognitive dysfunction, dizziness, and symptoms of overlapping conditions such as irritable bowel syndrome, headaches, and restless legs syndrome.¹ These
conditions can be grouped under the umbrella term of central sensitization syndromes (CSSs).\textsuperscript{2,3} Central sensitization (CS) is prevalent in chronic pain conditions and appears to be an important feature for the development and maintenance of many of these diseases, irrespective of other etiological aspects.\textsuperscript{4–6} The International Association for the Study of Pain (IASP) defines CS as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”.\textsuperscript{7} Diagnosis of CS often involves a review of medical records and an assessment of behavior, emotional disposition, and overall sensitivity of a patient.\textsuperscript{8} Obviously, these assessments are unable to directly capture the responsiveness of nociceptive neurons.\textsuperscript{9} There have been many different attempts to objectively quantify CS,\textsuperscript{10} including quantitative sensory testing (QST)\textsuperscript{11} and imaging techniques.\textsuperscript{10} However, these tools are complex, time-consuming, and expensive.\textsuperscript{11}

Self-report questionnaires would make a pragmatic alternative assessment of CS in everyday clinical practice, allowing for a quick and convenient assessment at little cost. To serve this purpose, however, these questionnaires would need to demonstrate acceptable associations with known measures of CS to show sufficient construct validity.\textsuperscript{12} Two such self-report questionnaires that are used in the assessment of CS and pain sensitivity are the Central Sensitization Inventory (CSI)\textsuperscript{13} and the Pain Sensitivity Questionnaire (PSQ).\textsuperscript{14} The CSI was designed to identify patients who have symptoms that may be related to CSS, such as FM.\textsuperscript{15} It has been shown to be a reliable and valid psychometric instrument for identifying individuals vulnerable to pain.\textsuperscript{13,16} A systematic review has shown that the CSI has strong psychometric properties, (ie, test–retest reliability, internal consistency, construct validity, criterion validity, cross-cultural validity, and content validity), according to the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist.\textsuperscript{17}

The goal of this study was to explore additional evidence of convergent and discriminant validity of the CSI in a large sample of subjects with FM. To test convergent validity, we hypothesized that CSI scores would be significantly correlated with other FM measure patient status, progress, and outcomes such as the FIQR,\textsuperscript{18} the modified Fibromyalgia Assessment Status questionnaire (modFAS),\textsuperscript{19} and the Polysymptomatic Distress Scale (PDS).\textsuperscript{20} To test discriminant validity, we hypothesized that CSI scores would be different among various FM severity states, with presumably different levels of CS. Furthermore, we hypothesized that these clinical variables would increase in severity as CSI scores increased, after the patients were organized into FM severity groups.

**MATERIALS AND METHODS**

**Study design and subjects**

From October 2020 to November 2021, FM patients were consecutively enrolled at a tertiary level Italian rheumatologic center in this observational cross-sectional study. All the patients underwent a complete physical examination specified in the revised European League Against Rheumatism (EULAR) recommendations for the management of FM.\textsuperscript{21} The inclusion criteria were: age from 18 to 80 years and a diagnosis of FM based on the 2016 revision to the 2010/2011 FM diagnostic criteria of the American College of Rheumatology (ACR),\textsuperscript{22} made by a rheumatologist with at least 20 years of experience. Patients were included regardless of the kind of treatment. Patients with diseases of the central or peripheral nervous systems (ie, Alzheimer’s disease or other dementias, Parkinson’s disease, motor neuron disease, polyneuropathy, multiple sclerosis, spinal lesions), with life-threatening conditions (ie, heart failure, active neoplasms, chronic renal failure), or with conditions that may interfere the clinimetric assessment (ie, symptomatic osteoarthritis, inflammatory arthropathies) were excluded. Just the interviewer and the subject were present during the interviews, which took place in a private room behind closed doors. The confidentiality of the participants was respected. The information gathered was only available to the investigators. All patients who took part in the study signed an informed consent document to undergo the study’s evaluation. The study procedures were approved by the local ethics committee.

**Measurements**

All patients were asked to complete a package of questionnaires about their sociodemographic data (age, sex, marital status, and education), disease-related variables, their quality of life, and the type(s) of pharmacological and nonpharmacological treatments currently received. The data and measures were electronically entered into the web-based Italian Fibromyalgia Registry (IFR).\textsuperscript{23}

Three disease-specific severity measures, the FIQR, the modFAS, and the PDS, with validated disease severity cutoff, were utilized to discriminate between severity states for FM. The CSI was used in the assessment of CS and pain sensitivity.

**Revised Fibromyalgia Impact Questionnaire**

The FIQR is a more recent variant of the FIQ.\textsuperscript{18} It is made up of 21 items with 11-point numerical rating
scales (NRS) that look at three major health domains (function, overall health status, symptoms) in relation to the previous week. The total score (range 0–100, with higher values suggesting greater severity) is calculated by summing the scores derived from the three subscales: the algebraic sum of the 9-item function domain (range 0–90) is divided by three, the algebraic sum of the 2-item general health domain (range 0–20) is taken as it is, and the algebraic sum of the 10-item symptom domain (range 0–100) is divided in half. The severity states for FIQR were determined by combining the mean 75th and 25th percentiles of adjacent severity categories: 0–23 for remission, 24–40 for mild disease, 41–63 for moderate disease, 64–82 for severe disease, and 83–100 for very severe disease.

**Modified Fibromyalgia Assessment Status**

The modFAS is the updated version of the Fibromyalgia Assessment Status (FAS) questionnaire, a patient-administered questionnaire comprising two sections. The first section contains two 11-point NRS (with the anchors 0 = no problem, 10 = severe problems) on fatigue and unrefreshing sleep, recalling the past week. The scores are summed with a maximum score of 20. The second section comprises a widespread pain index (WPI) that assesses 19 areas of the body and the patient should show where he or she had pain in the past week. The number of separate pain sites are summed (score 0–19). The final score of the modFAS is the sum of the two sections and ranges from 0 to 39. The application of calculated cutoff points for modFAS resulted in the following values: 0–12 for remission, 13–20 for mild disease, 20–28 for moderate disease, 29–33 for severe disease, and 34–39 for very severe disease.

**Polysymptomatic Distress Scale**

The PDS is derived from variables used in the 2010 ACR FM criteria modified for survey and clinical research. For the ACR diagnostic criteria, a diagnosis of FM can be made when levels of the WPI and Symptom Severity Scale (SSS) are sufficiently high (WPI ≥7 and SSS ≥5 or WPI 3–6 and SSS ≥9). The WPI is a 0–19 count of painful nonarticular body regions and the SSS is a 0–12 measure of symptom severity that includes fatigue, sleep, and cognitive problems. The PDS is obtained by summing the two components of the ACR criteria, the WPI and SSS (range 0–31). It was found that an FS ≥13 (out of a possible 31) provided a specificity of 91.8% and a sensitivity of 96.6% for a diagnosis of FM. Proposed PSD severity categories are: 0–3 for remission, 4–7 for mild severity, 8–11 for moderate severity, 12–19 for a severe disease, and 20–31 for a very severe disease.

**Central Sensitization Inventory**

The CSI is a screening tool designed to detect symptoms related to CS by measuring the degree of related phenomena. The CSI consists of two parts, of which part A includes 25 items about CS-related symptoms, scored on a 5-point Likert scale from 0 to 4. Higher total scores reflect higher CS symptomatology, whereas a 40-point score out of 100 was described as the cutoff value indicative for CS. Based on CSI score means and standard deviations from previously published subject samples, the following CSI severity levels were established: subclinical = 0–29; mild = 30–39; moderate = 40–49; severe = 50–59; and extreme = 60–100. Patients with CSI scores at least moderate were classified as having CSS. Those with scores indicating mild were classified as having mild CSS. Those with scores indicating subclinical was classified as not having CSS. Part B evaluates previously diagnosed CS-related disorders and was not considered in this study. The Italian CSI showed excellent construct validity, a good discriminative power, and excellent test–retest reliability.

**Statistical analysis**

Data were analyzed using 64-bit MedCalc®, version 19.0.1.0 (MedCalc Software). The normal distribution was tested with the Kolmogorov–Smirnov test. As recommended by Neblett and colleagues, the sample was classified into five CSI severity subgroups for further analysis. Where appropriate, the percentage differences between the groups were examined using a chi-square or Fisher’s exact test. The Mann–Whitney U test was used to compare continuous variables among categories of grouped data. To test the convergent validity, the Spearman’s rho was used to measure the degree of correlation between the variables CSI and the FM-specific measures (FIQR, modFAS, and PDS score). The strength of the correlation was interpreted by using Cohen’s criteria (large ≥0.50, medium = 0.30–0.49, and small = 0.10–0.29). To assess discriminant validity, CSI scores were grouped according to those of disease severity defined by the FIQR (remission, mild disease, moderate disease, severe disease, and very severe disease), and differences between these groups studied by means of the Kruskal–Wallis test, with Dunn’s tests for post hoc comparisons. In addition, in accordance with the categorization of the FIQR, interpretative cutoffs were proposed for the CSI, applicable to FM, using the
technique of reconciliation of the interquartile range of adjacent categories. Briefly, this technique is based on calculating the arithmetic mean (rounded to the nearest whole number) between the 75th percentile of the lower category with the 25th percentile of the upper category. The result represents the interpretive cutoff in the transition between categories.

The p values <0.05 were considered statistically significant.

RESULTS

Demographic data and CSI and FM-specific measures

The final analysis was conducted on 562 FM patients, 511 (90.1%) female. Table 1 presents the sociodemographic and clinical characteristics of the patients. Total mean score (standard deviation [SD]) of the CSI was 32.7 (16.8), 45.5 (21.9) for FIQR, 15.7 (8.2) for PDS score, and 21.6 (9.5) for modFAS.

CSI distribution and severity subgroups

Of the 562 FM patients, 199 (35.4%) were classified as having CSS with CSI scores ≥40. The number (percentage) of patients in each CSI severity subgroup were: subclinical 254 (45.1%), mild 109 (19.39%), moderate 93 (16.54%), severe 52 (9.25%), and extreme 54 (9.60%). The extreme CSI severity group had a significantly longer duration of pain than the subclinical, mild, and moderate severity groups (p = 0.001).

The CSI items linked to fatigue/sleep problems (CSI-1, CSI-8, and CSI-12) and muscle pain/tension (CSI-2 and CSI-18) had the highest ratings (greatest impact). The middle score areas were bruxism (CSI-4), gastrointestinal issues (CSI-5), (CSI-12), and headaches (CSI-10). Past childhood traumas were among the lowest scoring categories (CSI-24) (Table 2, Figure 1).

Convergent validity and correlations among FM-specific measures and CSI

Table 3 presents the correlations coefficients between the CSI score in the patient sample and scores on the other FM-specific measures. CSI was largely correlated with modFAS (ρ = 0.580; p<0.0001) (Figure 2A), FIQR (ρ = 0.542; p<0.0001) (Figure 2B), and PDS (ρ = 0.518; p<0.0001) (Figure 2C). The correlations between the CSI and the sociodemographic variables were nonsignificant.

Divergent validity and interpretability

In accordance with the disease severity categories of the FIQR, 121 patients were in remission, 125 in mild severity, 181 in moderate severity, 114 in severe disease, and 21 in very severe disease. The differences between the CSI scores in accordance with the FIQR disease severity states were significant (p<0.000001, Kruskal–Wallis test) (Table 4).

Applying the interquartile range reconciliation technique, the CSI cutoffs were: 21 in the transition from remission to mild severity, 30 in the transition from mild- to- moderate severity, 37 in the transition between moderate and severe disease, and 51 (rounding of 51.25) in the transition between severe and very severe disease.

| Table 1 | Demographic and clinimetric data |
|---------|---------------------------------|
|          | Mean   | Median | SD   | 25th–75th percentiles |
| Age (years) | 52.99  | 53.00  | 9.64 | 46.00–60.00           |
| BMI (kg/m2) | 26.28  | 26.60  | 2.58 | 24.50–27.80           |
| Educational level (years) | 3.01   | 3.00   | 0.93 | 2.00–4.00            |
| FIQR overall impact subscore | 8.34   | 8.00   | 5.55 | 3.00–13.00           |
| FIQR physical function subscore | 12.04  | 12.00  | 6.84 | 6.00–17.25           |
| FIQR symptoms subscore | 25.21  | 26.00  | 11.29 | 16.00–35.00         |
| FIQR | 45.50  | 45.00  | 21.91 | 27.00–63.00          |
| PDS | 15.76  | 16.00  | 8.23 | 8.00–23.00           |
| SSS | 5.79   | 5.00   | 4.22 | 2.00–10.00           |
| WPI | 9.96   | 9.00   | 4.92 | 6.00–14.00           |
| CSI | 32.76  | 31.00  | 16.85 | 19.00–45.00         |
| modFAS | 21.65  | 22.00  | 9.52 | 13.00–30.00         |

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; FIQR, revised Fibromyalgia Impact Questionnaire; modFAS, modified Fibromyalgia Assessment Status; PDS, Polysymptomatic Distress Scale; SD, standard deviation; SSS, Symptom Severity Scale; WPI, Widespread Pain Index.
DISCUSSION

In this study, the validity of the CSI in assessing FM patients in relation to key disease-specific clinimetric indices was demonstrated. Interpretative CSI cutoffs applicable to FM patients in the distinction of disease severity states have also been proposed.

Pain and heightened sensitivity to a variety of stimuli are the major complaints in FM patients. In this study, it has been shown that symptoms suggestive of CS are a very frequent condition in patients with FM, affecting 35.4% of them (CSI ≥40). In FM, the importance of central nervous system (CNS) dysregulation in stimuli processing is well documented. The central augmentation mechanisms of pain and sensory processing have been identified mainly using functional neuroimaging techniques.29–32 FM is a well-known CSS.33 CS refers to hypersensitivity of the CNS, resulting in enhancement of pain sensations.4 The IASP describes CS as increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input.34

Accumulating evidence suggests that CS could be also driven by neuroinflammation in the peripheral and CNS. A characteristic feature of neuroinflammation is the activation of glial cells (microglia and astrocytes) leading to the release of proinflammatory cytokines and chemokines.35,36

Detecting CS is a major challenge for physicians treating chronic pain conditions, and requires standardized protocols. Diagnosis involves the assessment of behavior, emotional disposition, overall sensitivity, and also a review of medical records of a patient. To date, there is no conclusive method of establishing the presence of CS, though QST is used to assess the dynamic modulation of nociceptive signals, which can suggest the presence of CS.37 Even though QST allows for a comprehensive assessment of pain sensitivity profiles, it needs select training, costly laboratory equipment, and is time expensive. These features make QST difficult at a clinical level in daily practice.38

CSI, a self-report measure, was developed as a screening instrument to inform clinicians that presenting symptoms may be related to CS.39 Previous

| Item | Item description | Mean | SD |
|------|------------------|------|----|
| CSI-1 | I feel tired and unrefreshed when I wake from sleeping | 2.04 | 1.11 |
| CSI-2 | My muscles feel stiff and achy | 2.28 | 1.05 |
| CSI-3 | I have anxiety attacks | 1.07 | 1.25 |
| CSI-4 | I grind or clench my teeth | 1.51 | 1.18 |
| CSI-5 | I have problems with diarrhea and/or constipation | 1.51 | 1.26 |
| CSI-6 | I need help in performing my daily activities | 0.96 | 1.20 |
| CSI-7 | I am sensitive to bright lights | 1.01 | 1.15 |
| CSI-8 | I get tired very easily when I am physically active | 2.01 | 1.18 |
| CSI-9 | I feel pain all over my body | 1.28 | 1.14 |
| CSI-10 | I have headaches | 1.50 | 1.12 |
| CSI-11 | I feel discomfort in my bladder and/or burning when I urinate | 0.89 | 1.15 |
| CSI-12 | I do not sleep well | 2.02 | 1.19 |
| CSI-13 | I have difficulty concentrating | 1.23 | 1.11 |
| CSI-14 | I have skin problems such as dryness, itchiness, or rashes | 1.35 | 1.18 |
| CSI-15 | Stress makes my physical symptoms get worse | 1.22 | 1.15 |
| CSI-16 | I feel sad or depressed | 1.13 | 1.09 |
| CSI-17 | I have low energy | 1.24 | 1.05 |
| CSI-18 | I have muscle tension in my neck and shoulders | 2.16 | 1.23 |
| CSI-19 | I have pain in my jaw | 0.97 | 1.20 |
| CSI-20 | Certain smells such as perfumes make me feel dizzy and nauseated | 1.00 | 1.12 |
| CSI-21 | I have to urinate frequently | 1.14 | 1.16 |
| CSI-22 | My legs feel uncomfortable and restless when I am trying to go to sleep at night | 1.23 | 1.20 |
| CSI-23 | I have difficulty remembering things | 1.10 | 1.04 |
| CSI-24 | I suffered trauma as a child | 0.82 | 1.14 |
| CSI-25 | I have pain in my pelvic area | 1.49 | 1.21 |

Abbreviations: CSI, Central Sensitization Inventory; SD, standard deviation.
researches demonstrated the validity of multiple language versions of the CSI, including Italian, through its associations with subjective and objective CS-related variables. Construct validity was evaluated in various studies. 16,27,40

In this study, the discriminant validity and the convergent validity of the Italian version of the CSI in patients with FM presenting different levels of CS, by assessing its association with three FM-specific measures (ie, FIQR, modFAS, and PDS) has been investigated.

To investigate the score distribution and validity of the CSI, the patient sample was divided into five severity subgroups (from subclinical to extreme) according to the previously recommended cutoffs. 27 The fact that scores were significantly different among all FM severity subgroups provides some support for the discriminant validity and clinical usefulness of these cutoffs. The sample distribution was somewhat skewed toward the lower severity ranges, with approximately 65% of the patients scoring below 40 (subclinical and mild severity ranges) and 19% scoring in the severe and extreme ranges. The extreme severity group had a significantly longer duration of pain than the subclinical, mild, and moderate severity groups, and the severe and extreme severity groups reported higher current pain, and mean pain over the last 4 weeks, compared to the other groups.

Although the already published cutoffs are valid, they were made by globally considering multiple conditions characterized by CS (eg, FM, chronic fatigue syndrome, irritable bowel syndrome), 27 potentially very different in terms of clinical expressions. In this study, others obtained on the basis of the disease severity categories of the FIQR were proposed. These cutoffs apply specifically to patients with FM as they were made exclusively from a case series of patients with this condition.

Previous studies have revealed that higher CSI scores in chronic pain samples were associated with higher pain severity, longer duration of pain, and female gender. 13,27 Convergent validity was demonstrated by the significant correlations ($p < 0.0001$) with disease-specific indicators (FIQR, modFAS, and PDS score).

The CSI items related to muscle pain/tension (CSI-2 and CSI-18) and fatigue/sleep problems (CSI-1, CSI-8, and CSI-12) had the highest scores, and these results were somewhat expected. CS refers to hypersensitivity of the CNS, resulting in enhancement of pain sensations. 4 CS is clinically and physiologically characterized by hyperalgesia (excessive sensitivity to a normally painful stimulus), allodynia, expansion of receptive field (that is likely to explain widespread pain), a prolonged electrophysiological discharge (that may explain the chronic nature of pain), and an after-stimulus unpleasant pain (eg, burning, throbbing, and paresthesia) that lasts longer than that observed in normal controls following a noxious stimulus. Because of the remarkable overall hyperexcitement of the central neurons, CS may explain the hypersensitivity to many environmental (eg, noise, weather, stress), and chemical (eg, pesticides and medications) stimuli. CS becomes self-sustained without further stimuli, even minor, because of long-term CNS neuroplasticity, and is probably accentuated with chronicity in human diseases.

Fatigue is common in FM, occurring in 80%–90% of the patients, and may be a more prominent symptom than pain in some patients. Fatigue in FM is of central origin, but peripheral factors such as muscle deconditioning may also be a contributory factor. There is some evidence that CS may contribute to fatigue. Fatigue is correlated with depression and poor sleep quality, and the previous day’s pain and poor sleep predicted the next day’s fatigue. However, morning fatigue may be a better indicator of nonrestorative sleep, and their relationship may be bidirectional. 41

There were several limitations to this study. First, our results are only based on the FM patient group. Hence, the findings might not be generalized to other CSSs.

**TABLE 3** Correlations (Spearman’s rank correlation coefficient) among fibromyalgia-specific measures and CSI

|       | modFAS | FIQR | PDS |
|-------|--------|------|-----|
| CSI   | 0.580  | 0.542| 0.518|
|       | <0.0001* | <0.0001* | <0.0001* |
| modFAS| 0.890  | 0.900| <0.0001*|
|       | <0.0001* | <0.0001* | |
| FIQR  | 0.863  | 0.863| <0.0001*|

Abbreviations: CSI, Central Sensitization Inventory; FAS, Fibromyalgia Assessment Scale; FIQR, revised Fibromyalgia Impact Questionnaire; PDS, Polysymptomatic Distress Scale.

*p values.

FIGURE 1 Spydergrams of the scores of the individual CSI items.
However, no previous studies evaluated the convergent validity of the CSI with disease-specific measures such as the FIQR, the modFAS, and the PDS. Moreover, the current study included a large patient sample, which allows a better use of CSI in FM patients. As a second limit, since there is no gold standard for the objective

**TABLE 4** Distribution of CSI in accordance with FIQR disease severity states and comparison (Kruskal–Wallis test)

| Disease severity states (FIQR) | n  | Median CSI score | Minimum CSI score | Maximum CSI score | 25th Percentile CSI score | 75th Percentile CSI score |
|-------------------------------|----|------------------|-------------------|-------------------|---------------------------|---------------------------|
| Remission                    | 121| 18.00            | 3.00              | 47.00             | 12.75                     | 25.25                     |
| Mild                         | 125| 29.00            | 5.00              | 55.00             | 16.75                     | 34.00                     |
| Moderate                     | 181| 38.00            | 3.00              | 74.00             | 26.00                     | 47.00                     |
| Severe                       | 114| 45.50            | 8.00              | 70.00             | 27.00                     | 61.00                     |
| Very severe                  | 21 | 55.00            | 15.00             | 75.00             | 41.50                     | 61.00                     |

**Kruskal–Wallis test**

- Test statistic: 150.1174
- Corrected for ties Ht: 150.1872
- Degrees of freedom: 4
- Significance level: \( p < 0.000001 \)

Abbreviations: CSI, Central Sensitization Inventory; FIQR, revised Fibromyalgia Impact Questionnaire.
detection of disorders of pain processing in humans, it is virtually impossible to adequately test construct validity for the CSI. In these circumstances, the validity has to be tested in other ways, as was done in this study. A third limitation may be the omission to consider the presence of comorbidities potentially associated with FM and also characterized by CSS. However, in this case study, the dominant clinical problem was the presence of FM.

In conclusion, the results of this study support the use of the CSI in FM patients, demonstrating the validity of the tool in this condition, contributing to its assessment and treatment planning. Future research on the CSI should focus on comparison with other relevant measures to detect altered central nociceptive processing, the ability of the CSI to recognize early symptoms of developing chronic pain states, and the assessment of progression in the rehabilitation of FM patients.

AUTHOR CONTRIBUTIONS
FS, PSP, and MDC contributed to the study conceptualization. FS and SF carried out data curation. FS and MDC did the formal analysis. FS, MDC, CM, SF, and PSP investigated the study. FS contributed to methodology and project administration. FS, MDC, and SF wrote the original draft. FS, PSP, and MDC contributed to writing – review and editing.

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CONFLICT OF INTEREST
No conflict of interests to be declared.

DATA AVAILABILITY STATEMENT
Study data are available upon reasonable request to the corresponding author.

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