

Brief Communication



Exploring Traits Associated With Central Sensitization Features in Patients With Chronic Cough

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ABSTRACT

The concept of cough hypersensitivity suggests that central sensitization plays a role in the pathophysiology of chronic cough. However, it remains unclear which traits are associated with central sensitization features in patients with chronic cough. A cohort of 317 Korean patients with newly referred chronic cough underwent clinical evaluations. The Central Sensitization Inventory (CSI), a questionnaire originally developed as a screening tool to identify patients with Central Sensitization Syndrome, was also administered. Other patient-reported outcomes (PROs), such as the cough severity visual analogue scale, Leicester Cough Questionnaire (LCQ), Cough Hypersensitivity Questionnaire (CHQ), and the Center for Epidemiological Studies Depression (CES-D) scale, were also administered. Follow-up assessments were conducted one month later. At baseline, the presence of CSI scores of ≥ 40 was associated with being female (89.6% vs. 63.4%; $P < 0.001$), older age, concomitant symptoms, and cough-related complications. CSI scores correlated with PRO scores, including LCQ ($r = -0.424$, $P < 0.001$), CHQ ($r = 0.373$, $P < 0.001$), and CES-D ($r = -0.660$, $P < 0.001$). Their patterns of correlations were similar in the 1-month longitudinal follow-up data analysis. In conclusion, CSI scores

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in patients with chronic cough correlated with cough-specific and depression-related PROs, suggesting the potential relevance of central sensitization in certain phenotypes of chronic cough.

Keywords: Cough; hypersensitivity; patient-reported outcome; phenotype

INTRODUCTION

Chronic cough, defined as a cough lasting 8 weeks or longer, imposes a considerable epidemiological burden¹ with a substantial impact on quality of life (QoL).²⁻⁵ The concept of cough hypersensitivity syndrome defines chronic cough as a clinical entity characterized by sensitization of the cough reflex.^{6,7} Recent studies have highlighted the central neural mechanisms of cough, supported by functional magnetic resonance imaging studies and successful treatment with centrally-acting neuromodulatory drugs (such as opioids, gabapentin, or pregabalin).^{8,13} Nevertheless, the imaging technologies are very sophisticated and not available outside specialist research centers, and their clinical translation is still warranted. Furthermore, it is unknown which traits or specific characteristics of patients with chronic cough are associated with central sensitization.

The Central Sensitization Inventory (CSI) is a questionnaire originally developed as a screening tool to identify patients with central sensitization pain syndrome.¹⁴ The syndrome describes a group of disorders related to central sensitization, such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome, which are typically characterized by hypersensitive pain sensation. However, to date, no studies have explored the relevance of CSI in patients with chronic cough. The present study aimed to explore clinical characteristics related to the CSI score in patients with chronic cough and examine the correlations of CSI with cough- and health-related patient reported outcomes (PROs).

MATERIALS AND METHODS

Study participants

This study analyzed newly referred chronic cough patients participating in the Korean Chronic Cough Registry study, a prospective multi-center observational cohort of adult patients recruited from referral allergy, pulmonology, or cough clinics across Korea.¹⁵ The baseline cohort profile and study protocols have been previously described.¹⁵ For study inclusion, subjects were Korean adults aged ≥ 19 years old, newly referred with active chronic cough. The exclusion criteria were as follows: (1) patients who were already managed for refractory chronic cough; (2) the presence of red-flag signs that may indicate other acute severe illness, such as hemoptysis, severe dyspnea, fever, or a history of recurrent pneumonia; (3) abnormal findings on physical examinations or chest X-rays indicating a potentially serious medical condition; and (4) other currently active medical conditions, such as malignancy, heart failure, stroke, or other severe respiratory diseases. All study participants provided written informed consent. The study protocols were approved by the Institutional Review Board of each participating institution (AMC IRB No. 2019-0754).

Baseline assessment

Baseline evaluation items include demographic and clinical characteristics for the patients such as age, sex, body mass index, smoking history, and physician-diagnosed medical

history. The presence of cough-associated symptoms and complications was evaluated based on patients' self-reports (yes or no).¹⁵

Cough-specific PROs included the cough severity visual analogue scale (VAS), a Korean version of the Leicester Cough Questionnaire (LCQ) to assess cough-specific QoL,¹⁶ and the Cough Hypersensitivity Questionnaire (CHQ) to evaluate cough triggers and cough-related laryngeal sensations. The cough VAS measured cough severity during the past week (0–100: 0 = no cough, 100 = worst cough). LCQ scores ranged from 3 to 21, with lower scores indicating greater impairment of cough-related QoL.¹⁶ The CHQ evaluated laryngeal sensations and cough triggers over the last 2 weeks with scores ranging from 0 to 22; higher scores reflected more frequent sensations or triggers.¹⁵ Depression was assessed by using the Korean version of the Center for Epidemiological Studies Depression (CES-D) scale questionnaire (score range: 0–60); higher scores indicated more severe depressive symptoms.⁵

Baseline diagnostic tests included results from chest X-rays, spirometry, and fractional exhaled nitric oxide (FeNO). Chest X-ray findings were considered abnormal when the radiologist identified any grossly abnormal parenchymal lesion.

Central sensitization inventory

In the present study, part A of the Korean version of the CSI questionnaire was utilized; it assessed 25 health-related symptoms commonly present in central sensitization syndrome, with each item scored on a scale from 0 (“never”) to 4 (“always”).¹⁷ A higher total score indicated a greater degree of patient-reported symptomatology, with a maximum score of 100. We employed a CSI cutoff value of ≥ 40 to define the presence of central sensitization pain syndrome, based on a validation study that reported 81% sensitivity and 75% specificity for the patients.¹⁸ Subjects were classified into 2 groups: CSI score ≥ 40 and < 40 , and their clinical and cough characteristics were compared.

One-month longitudinal follow-up

All the PRO scores were collected at the 1-month follow-up visit,¹⁵ while the study participants received management for chronic cough following international and national guidelines.^{19–21}

Statistical analyses

Descriptive data are presented as mean $\pm$ standard deviation, median with interquartile range (IQR), or percentages. Student's *t*-tests, Mann-Whitney tests, or χ^2 tests were used for group comparisons. Spearman's correlation tests were conducted to examine the associations among different PRO scores including CSI. Given the relationship between cough and depression,²² a multivariate linear regression analysis was performed to examine the association between cough and CSI score, adjusting for age, sex, and CES-D score. Statistical analyses were performed by using Stata software (version 17.0 for Mac; StataCorp, College Station, TX, USA). A 2-sided *P* value of < 0.05 was considered significant.

RESULTS

Study participants

A total of 317 study participants (mean age: 54.6 ± 15.1 , female sex: 67.5%) were analyzed. They were recruited from November 2021 to February 2023. The median total CSI score was 23 (IQR: 13–33) (**Fig. 1A**), with scores higher in females than in males (median 25 [IQR:

16–37] vs. median 17 [IQR 9–28], respectively; $P < 0.001$; **Fig. 1B**). Scores for each item are presented in **Fig. 1C**.

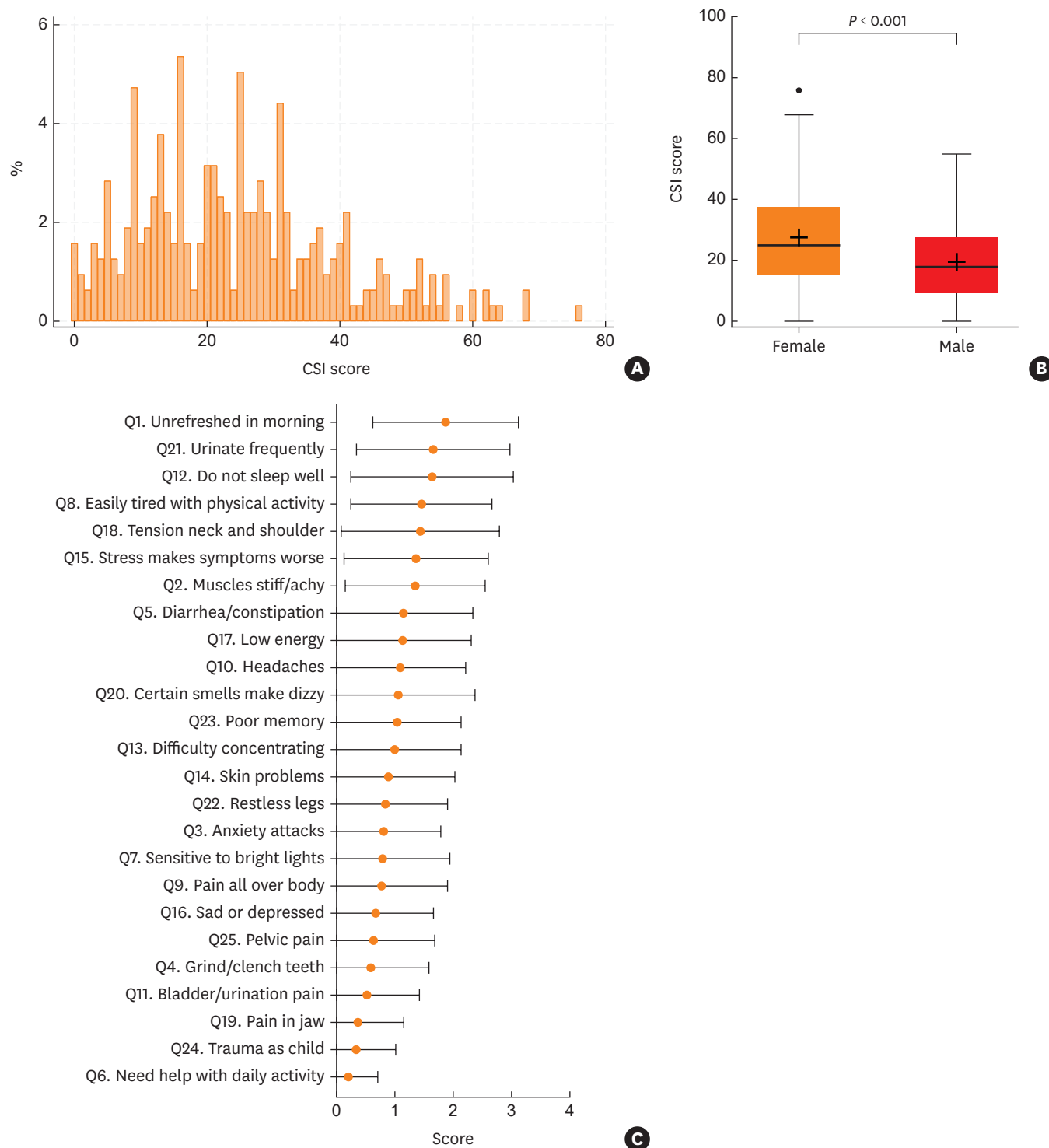


Fig. 1. (A) Histogram displaying the CSI questionnaire scores in patients with chronic cough. (B) Comparison of CSI scores according to sex; box indicates the lower and upper quartile; plus sign, mean value; central line, median value; and points at the ends of the whiskers, upper extreme values. (C) Scores for individual items on the CSI questionnaire (mean with standard deviation). CSI, Central Sensitization Inventory.

CSI score was ≥ 40 in 15.1% (48/317). Patients with CSI score ≥ 40 were older (mean age: 55.1 ± 15.0 vs. 51.3 ± 15.2 years, respectively; $P < 0.010$) and more frequently female (89.6% vs. 63.4%; $P < 0.001$) than those with CSI score < 40 (**Table 1**). Subjects with CSI score ≥ 40 exhibited a higher rate of concomitant symptoms, such as rhinorrhea (54.2% vs. 37.2%; $P = 0.027$), nasal obstruction (37.5% vs. 21.0%; $P = 0.013$), dyspnea (35.4% vs. 14.3%; $P < 0.001$), heartburn (27.1% vs. 10.9%; $P = 0.002$), regurgitation (27.1% vs. 13.2%; $P = 0.014$), and sputum (81.2% vs. 61.4%; $P = 0.008$), respectively. Cough-related complications were also more frequent in patients with CSI score ≥ 40 : fatigue (58.3% vs. 27.3%; $P < 0.001$), urinary incontinence (54.2% vs. 23.6%; $P < 0.001$), and headache (54.2% vs. 23.6%; $P < 0.001$), respectively. A physician-reported history of gastroesophageal reflux disease was more frequent in those with CSI score ≥ 40 (34.0% vs. 20.0%; $P = 0.033$). No significant differences in chest X-rays, spirometry, or FeNO concentrations were seen.

Table 1. Comparison of baseline characteristics of patients with chronic cough according to a CSI score cutoff of ≥ 40 ¹⁸

Characteristics	Total	CSI ≥ 40	CSI < 40	P value
No. of subjects	317	48	269	
Age (year)	54.5 ± 15.0	55.1 ± 15.0	51.3 ± 15.2	< 0.010
Female sex (%)	67.5	89.6	63.4	< 0.001
BMI (kg/cm ²)	24.8 ± 4.8	25.6 ± 5.6	24.6 ± 4.7	0.19
Smoking status (%)				0.10
Non-smoker	76.3	85.4	74.5	
Ex-smoker	19.3	8.3	21.3	
Current smoker	4.4	6.2	4.1	
Concomitant symptoms (%)				
Rhinorrhea	39.7	54.2	37.2	0.027
Nasal obstruction	23.4	37.5	21.0	0.013
Anosmia	5.7	6.2	5.6	0.86
Wheezing	16.7	23.4	15.5	0.18
Dyspnea	17.4	35.4	14.3	< 0.001
Heartburn	13.3	27.1	10.9	0.002
Regurgitation	15.2	27.1	13.2	0.014
Sputum	64.2	81.2	61.4	0.008
Snoring	18.7	27.7	17.2	0.09
Cough-related complications (%)				
Fatigue	32.0	58.3	27.3	< 0.001
Incontinence	28.2	54.2	23.6	< 0.001
Chest pain (or rib fracture)	26.6	35.4	24.7	0.12
Syncope	1.0	0.0	1.1	0.46
Headache	28.5	54.2	23.6	< 0.001
Hernia	0.3	0.0	0.4	0.67
Physician-diagnosed history (%)				
Hypertension	26.4	23.4	26.7	0.64
Diabetes	8.9	12.8	8.2	0.32
Tuberculosis	5.9	0.0	7.1	0.060
Cardiac arrhythmia	2.0	4.3	1.6	0.23
Heart failure	1.0	0.0	1.2	0.45
Autoimmune disorder	1.0	2.1	0.8	0.39
Thyroid disorder	6.3	2.2	7.1	0.21
GERD	22.1	34.0	20.0	0.033
Asthma	3.7	6.4	3.2	0.28
Laboratory findings				
Chest X-ray abnormality (%)	12.6	12.8	12.6	0.93
FEV1/FVC ratio	0.79 ± 0.13	0.78 ± 0.18	0.80 ± 0.12	0.38
FEV1% predicted (%)	0.89 ± 0.19	85.20 ± 24.80	90.10 ± 17.30	0.10
FVC% predicted (%)	0.88 ± 0.20	84.40 ± 24.80	88.50 ± 18.70	0.20
FeNO (ppb), median (IQR)	18 (11–28)	17 (12–30)	18 (11–28)	0.95

CSI, Central Sensitization Inventory; BMI, body mass index; GERD, gastroesophageal reflux disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; IQR, interquartile range.

Relationships between CSI and other PRO scores

Participants with CSI score ≥ 40 exhibited significantly higher cough severity VAS scores (median 70 [IQR: 40–80] vs. 55 [IQR: 40–70]; $P = 0.020$), lower LCQ scores (median 9.47 [IQR: 7.00–10.84] vs. 11.74 [IQR: 9.13–14.21]; $P < 0.001$), higher CHQ scores (median 10.5 [IQR: 7.5–14] vs. 8 [IQR: 5–11]; $P < 0.001$), and higher CES-D scores (median 23.5 [IQR: 16–30.5] vs. 5 [IQR: 2–12]; $P < 0.001$), respectively, compared to those with CSI score < 40 (Fig. 2).

In Spearman analyses, the CSI score correlated weakly with cough severity VAS ($r = 0.213$, $P < 0.001$), but more strongly with LCQ ($r = -0.424$, $P < 0.001$), CHQ ($r = 0.373$, $P < 0.001$), and CES-D ($r = -0.660$, $P < 0.001$) (Fig. 3). In sensitivity analyses excluding 9 CSI items potentially related to cough consequences/complications, such as fatigue, sleep disturbance, urinary symptoms, anxiety, or depression (Q1, Q3, Q8, Q10, Q11, Q12, Q16, Q17, and Q21), their correlations remains significant between CSI scores and LCQ ($r = -0.359$, $P < 0.001$), CHQ ($r = 0.327$, $P < 0.001$), and CES-D ($r = -0.563$, $P < 0.001$).

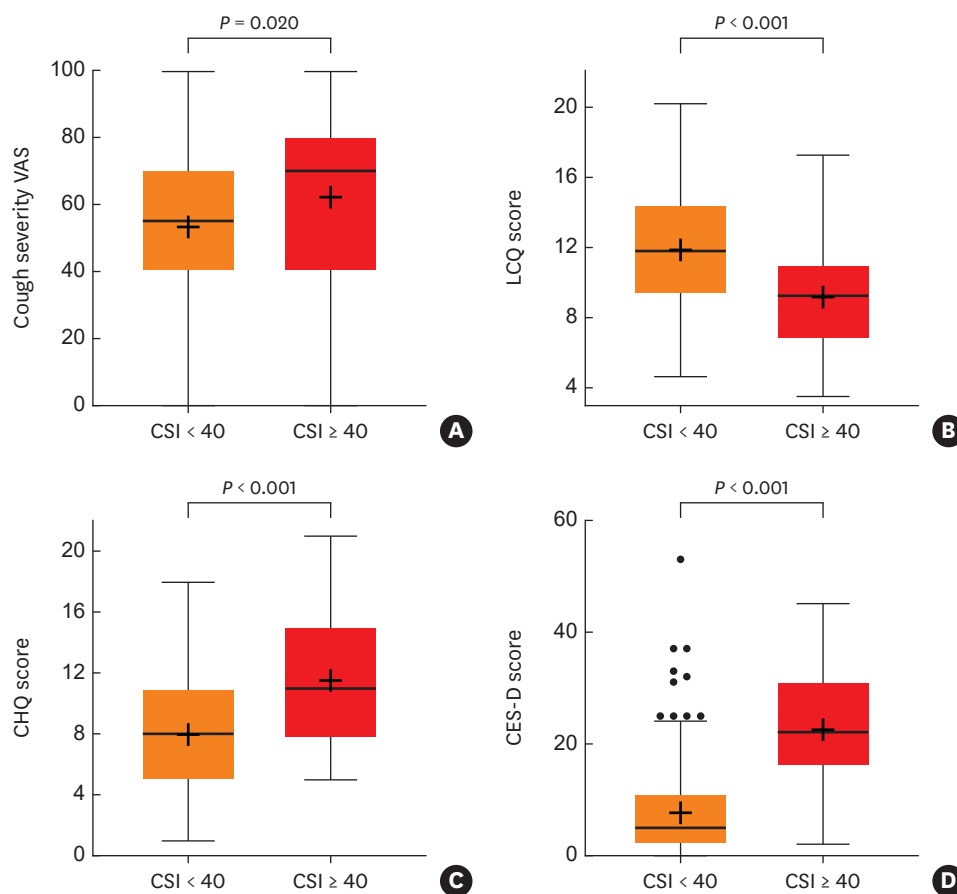


Fig. 2. Comparison of patient-reported outcomes based on a CSI score cutoff of ≥ 40 .¹⁸ Box indicates the lower and upper quartile; plus sign, mean value; central line, median value; and points at the ends of the whiskers, upper extreme values. (A) Cough severity VAS. (B) LCQ scores. (C) CHQ scores. (D) CES-D scores. CSI, Central Sensitization Inventory; VAS, visual analogue scale; LCQ, Leicester Cough Questionnaire; CHQ, Cough Hypersensitivity Questionnaire; CES-D, Center for Epidemiological Studies Depression.

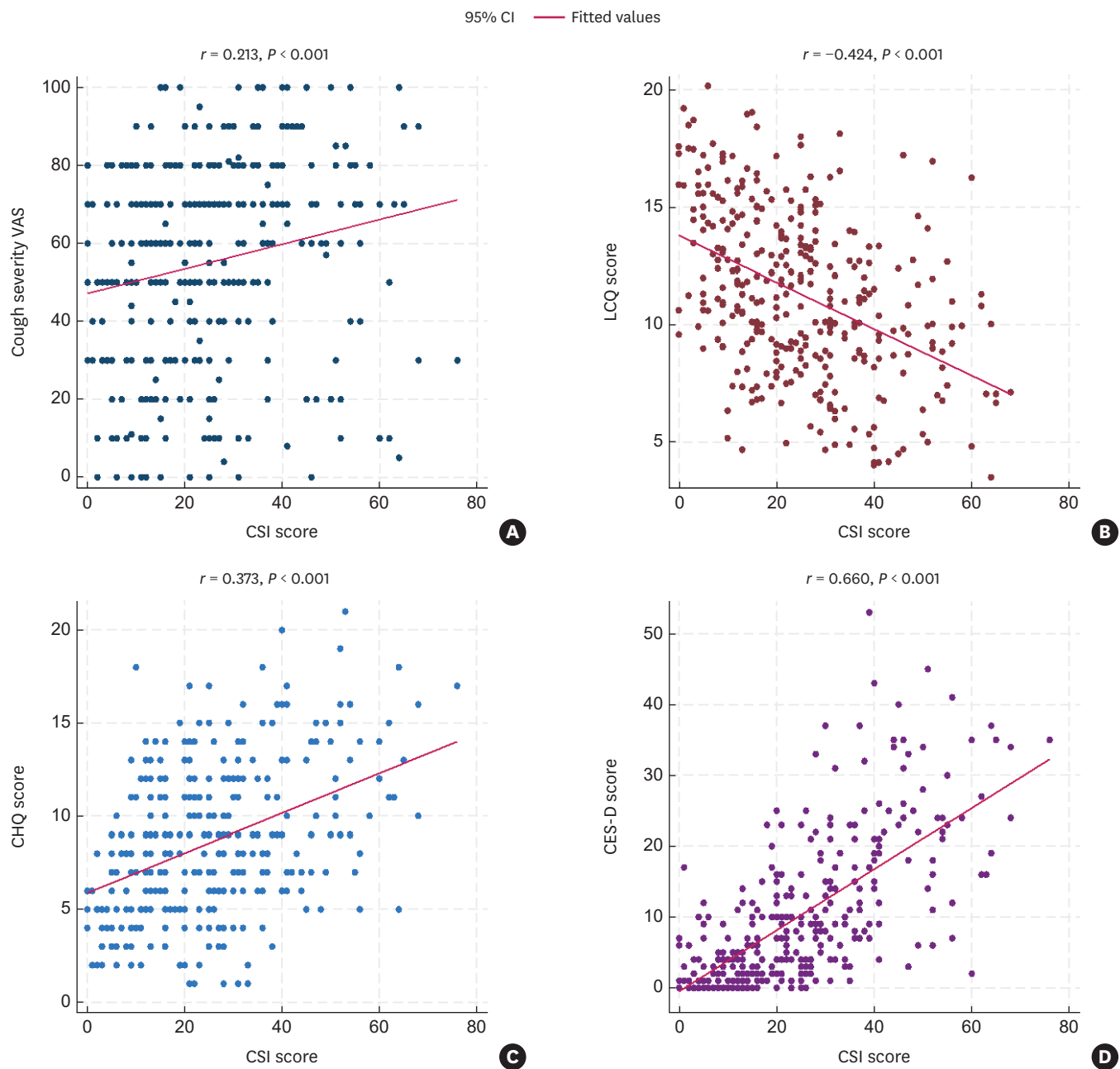


Fig. 3. Scatter dot plots illustrating correlations with the CSI questionnaire score. (A) Cough severity VAS. (B) LCQ scores. (C) CHQ scores. (D) CES-D scores. CSI, Central Sensitization Inventory; VAS, visual analogue scale; LCQ, Leicester Cough Questionnaire; CHQ, Cough Hypersensitivity Questionnaire; CES-D, Center for Epidemiological Studies Depression.

Considering the relationship between cough and depression,²² a multivariate linear regression analysis was conducted to examine the potential confounding effect of depression on the association of cough with the CSI score (or vice versa). The analysis indicated that both LCQ and CES-D scores significantly correlate with the CSI score, independent of co-adjusted parameters (**Table 2**).

Table 2. Multi-variate linear regression analysis for CSI scores

For CSI score (as a dependent variable)	Coefficient (95% CI)	P value
Age (year)	−0.091 (−0.174, −0.008)	0.032
Male sex (vs. female)	−0.439 (−7.126, −1.650)	0.002
LCQ score	−0.579 (−0.977, −0.181)	0.004
CES-D score	0.832 (0.695, 0.969)	< 0.001

CSI, Central Sensitization Inventory; 95% CI, 95% confidence interval; LCQ, Leicester Cough Questionnaire; CES-D, Center for Epidemiological Studies Depression.

One-month longitudinal follow-up data analysis

A total of 252 subjects completed the 1-month follow-up visit, while receiving management following international and national guidelines.^{19–21} The median CSI score at follow-up was 19 (IQR: 10–31), which significantly correlated with the score at baseline ($r = 0.701$, $P < 0.001$). Improvements were observed in PRO scores: the LCQ score increased from a median of 11.14 (IQR: 8.89–13.99) to 15.92 (IQR: 12.57–18.08), and the CHQ score declined from a median of 8 (IQR: 5–11) to 7 (IQR: 3–10). In addition, cough severity VAS score dropped from a median of 60 (IQR: 40–70) to 25 (IQR: 10–50), and the CES-D score decreased from a median of 7 (IQR: 2–15) to 4 (IQR: 1–9). In Spearman analyses, the change in CSI score significantly correlated with the change in LCQ score ($r = -0.311$, $P < 0.001$), CHQ score ($r = 0.257$, $P < 0.001$), and CES-D score ($r = 0.550$, $P < 0.001$), but not with the change in cough severity VAS ($r = -0.036$, $P = 0.711$).

DISCUSSION

This study explored traits related to CSI scores in newly referred patients with chronic cough. The CSI scores in our patient registry were median 23 (IQR: 13–33), which are lower than those reported in central sensitization pain syndromes (40–50), but similar to healthy controls (28.9).^{14,18} CSI score was ≥ 40 in 15.1% (48/317). Despite the relatively low CSI scores, the presence of CSI score ≥ 40 was associated with specific features in patients with chronic cough: female sex, older age, a higher incidence of concomitant symptoms, and more cough-related complications. Correlations of CSI scores with LCQ, CHQ, and CES-D scores were also observed, even after excluding potentially confounding CSI items (related to cough consequences such as fatigue, sleep disturbance, urinary symptoms, anxiety, and/or depression). These findings suggest that central sensitization features might be relevant to older female chronic cough patients with more diverse and severe symptoms, including depression.

An issue with the CSI is that it has not been validated to provide objective evidence of central sensitization in patients with chronic cough. The cutoff score of 40 was suggested based on a case-control study that compared patients with central sensitization pain syndrome with normal controls.¹⁸ Hence, an optimal threshold score warrants validation in patients with chronic cough. Therefore, our findings are exploratory in nature and do not directly confirm the presence of central sensitization but merely suggest its potential associations. Nevertheless, an important observation is that the CSI score revealed correlations with cough-specific PROs such as the LCQ and CHQ. Interestingly, the correlation between CSI and cough VAS scores were weaker (than LCQ or CHQ), which suggests that perception of cough severity alone may not determine the CSI response. Instead, symptoms associated with cough hypersensitivity or the perceived impact of cough on QoL might be more relevant.

Interestingly, we observed a strong correlation between the CSI and CES-D scores, even after excluding CSI questions related to anxiety and depression. Depression and chronic pain are interrelated²³; however, our observations might offer a clue that depression or susceptibility to it might underlie the link between chronic cough and central sensitization.

This study has some limitations. First, because the study population was recruited from referral clinics, external validity to general population may be limited. However, because we analyzed newly referred patients, our findings might be applicable to a similar clinical setting. The observed relatively low CSI score distribution may also be due to patient selection criteria that excluded those patients with other active medical conditions. Secondly, our study focused solely on subjective patient-reported cough profiles, without incorporating objective measures such as cough frequency or tussigen-induced cough reflex sensitivity, due to the nature of our real-world clinical practice-based study design. Thirdly, the presence of laryngeal dysfunction, a potential link to cough and central sensitization, was not investigated. The diagnostic procedure for laryngeal dysfunction was formally introduced in Korea in July 2022,²⁴ which was after the initiation of the registry study. Further investigation is needed whether chronic cough patients with high CSI scores could benefit from behavioral cough suppression therapy.²⁵ Despite these limitations, our study is the first to explore the potential of the CSI in evaluating cough profiles and its relationship with treatment response.

In conclusion, certain traits of patients with chronic cough, including female sex, older age, accompanying symptoms, and depression, greater cough impact on QoL, and more cough-related sensations/triggers (as represented by the CHQ score), were associated with higher CSI scores. These relationships suggest potential implications of central sensitization in elderly female patients with more diverse and severe symptoms, including depression. However, whether the CSI questionnaire can represent central sensitization in chronic cough remains to be determined.

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