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Brief Communication

Clinical Characteristics of Post-COVID-19 Persistent Cough in the Omicron Era

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ABSTRACT

Cough is one of the most common symptoms of acute coronavirus disease 2019, but cough may persist for weeks or months. This study aimed to examine the clinical characteristics of patients with post-coronavirus disease (COVID) persistent cough in the Omicron era. We conducted a pooled analysis comparing 3 different groups: 1) a prospective cohort of post-COVID cough (> 3 weeks; n = 55), 2) a retrospective cohort of post-COVID cough (> 3 weeks; n = 66), and 3) a prospective cohort of non-COVID chronic cough (CC) (> 8 weeks; n = 100). Cough and health status was assessed using patient-reported outcomes (PROs). Outcomes, including PROs and systemic symptoms, were longitudinally evaluated in the prospective post-COVID cough registry participants receiving usual care. A total of 121 patients with post-COVID cough and 100 with non-COVID CC were studied. Baseline cough-specific PRO scores did not significantly differ between post-COVID cough and non-COVID CC groups. There were no significant differences in chest imaging abnormality or lung function between groups. However, the proportions of patients with fractional exhaled nitric oxide (FeNO) ≥ 25 ppb were 44.7% in those with post-COVID cough and 22.7% in those with non-COVID CC, which were significantly different. In longitudinal assessment of the post-COVID registry (n = 43), cough-specific PROs, such as cough severity or Leicester Cough Questionnaire (LCQ) scores, significantly improved between visits 1 and 2 (visit interval: median 35 [interquartile range, IQR: 23–58] days). In the LCQ score, 83.3% of the patients showed improvement (change ≥ +1.3), but 7.1% had worsened (≤ −1.3). The number of systemic symptoms was median 4 (IQR: 2–7) at visit 1 but decreased to median 2 (IQR: 0–4) at visit 2. In summary, post-COVID persistent cough was similar in overall clinical characteristics to CC. Current cough guideline-based approaches may be effective in most patients with post-COVID cough. Measurement of FeNO levels may also be useful for cough management.

Keywords: Cough; COVID-19; asthma; Omicron era; cohort; longitudinal assessment; nitric oxide; post-COVID syndrome

Disclosure

W.-J.S. declares grants from Merck Sharp & Dohme Corp. and AstraZeneca, consulting fees from Merck, AstraZeneca, Shionogi and GSK, and lecture fees from Merck, AstraZeneca, GSK and Novartis. Other authors declare that they have no competing interests.

INTRODUCTION

Cough is one of the most common symptoms of acute coronavirus disease 2019, occurring in approximately 60% of patients.[1] However, in some individuals, cough may persist for weeks or months after recovery from COVID-19. Cough in acute and post-acute coronavirus disease (COVID) conditions not only causes physical distress but also has a negative social impact on patients, sometimes leading to social isolation.[2,3]

The phenomenon of long COVID (or post-COVID syndrome) was first reported in a cohort study in Italy in July 2020, and cough was the fifth most common symptom (16%).[4] In a meta-analysis of studies published in 2020, the estimated prevalence of persistent cough was 18% (95% confidence interval: 12%–24%; I^2 = 93%) in patients previously hospitalized for COVID pneumonia.[2] However, clinical characteristics of post-COVID persistent cough have not been reported in detail. Treatment recommendation has not been made for cough in the European Society of Clinical Microbiology and Infectious Diseases guidelines of long COVID.[5] In Korea, a practice guideline for long COVID has recently been published by the Korean Society of Infectious Diseases; however, there are no recommendations for cough in diagnostic tests or treatment strategies except chest imaging studies (chest radiography and computed tomography).[6]

In South Korea, the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected an unprecedented large number of people since 2022[7] and has become a predominant variant since February 2022.[8] We conducted a prospective registry study of patients with post-COVID cough in April of 2022, with an aim to investigate the clinical characteristics and longitudinal course. In this brief report, we analyzed their baseline cough and clinical characteristics as well as examined early treatment responses using cough-specific patient-reported outcomes (PROs).

MATERIALS AND METHODS

Study population

The present study was a pooled analysis comparing 3 different patient registries: 1) a prospective cohort of post-COVID persistent cough (post-COVID registry A), 2) a retrospective study of post-COVID persistent cough (post-COVID registry B), and 3) a prospective study of non-COVID chronic cough (CC).

(1) In the post-COVID registry A, patients with persistent cough (> 3 weeks) post-COVID-19 infection (confirmed polymerase chain reactions) were consecutively recruited from a cough clinic at a tertiary hospital in Seoul, Korea, between April and November of 2022. Exclusion criteria were 1) a history of CC prior to COVID-19 diagnosis and 2) current febrile illness. All participants received usual care according to current international and national cough guidelines.[9,10] The baseline and longitudinal data (visits 1 and 2) were analyzed.

(2) For external comparison, cross-sectional data from a retrospective registry of post-COVID persistent cough (>3 weeks) (post-COVID registry B) was analyzed. The data were collected from patients who visited a referral allergy and pulmonology clinic at a secondary hospital in Gwangmyeong, Korea, between March and August of 2022. No selection criteria were used except for having post-COVID persistent cough (>3 weeks).

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(3) For comparison of baseline clinical characteristics, cross-sectional data from 100 patients who developed CC (>8 weeks) before the COVID outbreak and were analyzed in the Korean Chronic Cough Registry study. They were prospectively recruited from a cough clinic at a tertiary hospital in Seoul, Korea. The details of selection criteria have previously been reported[11] and are described in **Supplementary Data S1**.

All participants in the prospective studies gave informed consent. Each of the prospective and retrospective study protocol was approved by the Institutional Review Board (IRB) (IRB No. 2019-0754, 2022-0552, and 2208-021-030).

Clinical parameters in the prospective studies

At baseline visit (V1), participants in post-COVID cough registry A and non-COVID CC registry were assessed for demographics, cough duration, comorbidity, and cough-specific PROs, including cough severity score (0–10, a higher score indicates a more severe cough), Leicester Cough Questionnaire (LCQ) (3–21; a lower score indicates more impact of cough on quality of life [QoL]),[12] cough hypersensitivity questionnaire (CHQ) (0–23; a higher score indicates more features of hypersensitivity),[13] and general health-related QoL questionnaires (EuroQol visual analogue scale [EQ-VAS] and EuroQol five-dimensional questionnaire [EQ-5D-5L] index). [14] Diagnostic test results (chest radiography, spirometry, and fractional exhaled nitric oxide [FeNO]) were also collected.

In the post-COVID cough registry A participants, systemic symptoms were evaluated. At their visit 2 (V2), cough and health-related PRO were repeatedly measured, which included cough severity score, LCQ, CHQ, EQ-VAS, and EQ-5D-5L index.

Clinical parameters in the retrospective cohort study

In the retrospective post-COVID registry B, medical records were reviewed for the following baseline parameters: demographics, cough duration, comorbidity, respiratory symptoms, and diagnostic test results (chest radiography, spirometry, and FeNO).

Statistical analysis

For descriptive statistics, data on continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR), and data on categorical variables are presented as frequency. Data normality was assessed by visual inspection of each parameter histogram. Parametric data were analyzed with Student's *t*-test for intergroup comparison. Nonparametric data were compared using the Mann-Whitney *U*-test. Categorical data were compared by the Chi-square test. Linear regression analyses were performed to examine associations between FeNO levels and baseline parameters; FeNO levels were log-transformed to normalize the distribution. In multivariate linear regression analyses, demographic variables (age, sex, and smoking history) and clinical parameters (asthma, allergic rhinitis, and wheezing) were adjusted. Longitudinal changes of PROs were assessed using the paired *t*-test. A two-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 121 patients with post-COVID persistent cough (55 from post-COVID registry A and 66 from post-COVID registry B) and 100 with non-COVID CC were studied (**Table 1**).

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Table 1. Baseline characteristics of the study participants at enrollment

Characteristics	Post-COVID cough (A) (n = 55)	Post-COVID cough (B) (n = 66)	Non-COVID CC (C) (n = 100)	*P* value (A vs. B)	*P* value (A vs. C)	*P* value (B vs. C)
Age (yr)	47.7 ± 15.9	47.1 ± 15.0	52.9 ± 14.6	0.846	0.040	0.015
Cough duration (wk)	Median 9 (IQR: 6–13)	Median 6.1 (IQR: 4–10.7)	Median 48 (IQR: 16–162)	0.014	< 0.001	< 0.001
Current CC (> 8 wk), %	60.0%	39.4%	100%	0.058	< 0.001	< 0.001
Female sex, %	63.6%	68.2%	64.0%	0.599	0.964	0.579
History of admission for COVID-19, %	3.6%	0.0%	NA	0.118	NA	NA
Smoking history, %						
Never smoker	74.6%	84.9%	77.0%	0.188	0.002	0.054
Former smoker	14.6%	12.1%	23.0%			
Current smoker	10.9%	3.0%	0%			
Self-reported previous medical history, %						
Asthma	15.1%	4.6%	3.0%	0.048	0.006	0.602
Allergic rhinitis	52.7%	18.2%	7.0%	< 0.001	< 0.001	0.027
Symptoms, %						
Sputum	67.3%	48.5%	47.0%	0.065	0.015	0.851
Dyspnea	58.2%	21.2%	6.0%	< 0.001	< 0.001	0.003
Wheeze	38.2%	10.6%	8.0%	< 0.001	< 0.001	0.566
Baseline diagnostic tests						
Chest image abnormality, %	10.6% (5/47)	17.2% (11/64)	16.5% (13/79)	0.332	0.367	0.907
PNS image abnormality, %	31.6% (6/19)	20.0% (12/60)	36.4% (8/22)	0.354	0.747	0.126
FEV1% of predicted	87.1 ± 12.3 (n = 54)	91.3 ± 15.8 (n = 47)	88.6 ± 13.0 (n = 70)	0.133	0.575	0.269
FVC% of predicted	87.8 ± 13.7 (n = 54)	92.4 ± 13.2 (n = 47)	86.8 ± 12.3 (n = 70)	0.079	0.670	0.017
FEV1/FVC ratio	80.0 ± 7.8 (n = 54)	82.2 ± 7.6 (n = 47)	82.0 ± 7.2 (n = 70)	0.142	0.134	0.866
FeNO levels (ppb)	Median 20 (IQR: 13–39)	Median 21.5 (IQR: 15–44)	Median 17 (IQR: 12–23)	0.363	0.096	0.003
FeNO ≥ 25 ppb, %	42.9% (21/49)	46.3% (25/54)	22.7% (22/97)	0.726	0.012	0.003

P values were determined by Student's *t*-test, the Mann-Whitney *U*-test, or the χ^2 test.
COVID, coronavirus disease; CC, chronic cough; IQR, interquartile range; COVID-19, coronavirus disease 2019; NA, not applicable; PNS, paranasal sinus; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide.

Only 2 patients in post-COVID registry A (3.6%) had a history of hospital admission for acute COVID-19 care. Compared with patients with non-COVID CC, those with post-COVID cough were younger and had shorter cough duration. However, there were no significant differences in sex. The proportions of current CC (>8 weeks) was 60.0% in post-COVID registry A and 39.4% in registry B at V1. Dyspnea, wheezing, and self-reported history of asthma and allergic rhinitis were more frequent was significantly more frequent in post-COVID registry A (58.2%, 38.2%, 15.1% and 52.7%, respectively) than in other groups (**Table 1**).

In baseline diagnostic tests, there was no significant difference in the proportion of patients with chest or paranasal sinus image abnormalities. All groups showed comparable pulmonary function. The baseline FeNO levels were significantly higher in patients with post-COVID cough registry B than in those with non-COVID CC (median 21.5 [IQR: 15–44] ppb vs. 17 [12–23] ppb; $P = 0.003$; **Table 1** and **Fig. 1A**). The proportion of patients with FeNO ≥ 25 ppb, a cutoff value for predicting treatment responses to steroids or type 2 biologics,[15,16] was 44.7% in patients with post-COVID cough (registry A: 42.9% and B: 46.3%), which was significantly higher than in those with non-COVID CC (22.7%) (**Table 1** and **Fig. 1B**).

In univariate linear regression analyses, wheezing and post-COVID cough showed significant associations with FeNO levels, but non-COVID CC did not. The relationships of post-COVID cough with FeNO levels were significant in multivariate regression analyses after adjustment for demographic parameters, history of asthma and allergic rhinitis, or wheezing, but non-COVID CC did not (**Table 2**). The associations between post-COVID cough and FeNO levels also remained significant in a subgroup analysis of 168 subjects without wheezing (data not shown).

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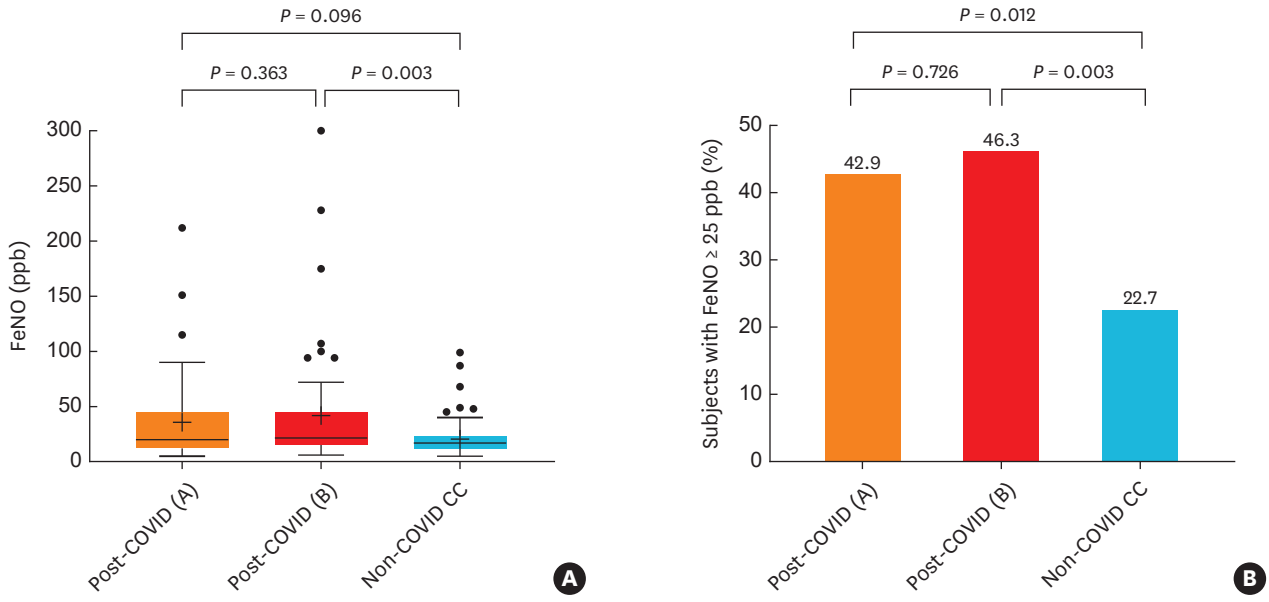

Fig. 1. FeNO levels at study enrollment. (A) FeNO levels; and (B) proportion of subjects with FeNO ≥ 25 ppb. Box indicates the lower and upper quartile; (+) sign, mean value; central line, median value; and points at the ends of the whiskers, upper extreme values. *P* values were determined by the Mann-Whitney *U*-test or the χ^2 test.
FeNO, fractional exhaled nitric oxide; COVID = coronavirus disease.

Table 2. Multivariate linear regression analyses for FeNO levels in the study subjects (N = 200)

For log-FeNO (ppb)*	Univariate		Multivariate (model 1)†		Multivariate (model 2)‡	
	Correlation coeff. (95% CI)	*P* value	Correlation coeff. (95% CI)	*P* value	Correlation coeff. (95% CI)	*P* value
Age (yr)	0.000 (−0.003, 0.003)	0.886	0.001 (−0.002, 0.004)	0.516	0.001 (−0.002, 0.004)	0.398
Male sex (vs. female)	0.719 (−0.025, 0.168)	0.144	0.028 (−0.088, 0.144)	0.635	0.023 (−0.091, 0.137)	0.690
Former smoker (vs. never)	0.085 (−0.035, 0.205)	0.166	0.088 (−0.053, 0.229)	0.218	0.086 (−0.051, 0.224)	0.218
Current smoker (vs. never)	0.225 (−0.011, 0.461)	0.061	0.109 (−0.162, 0.380)	0.428	0.098 (−0.154, 0.350)	0.443
Self-reported previous history of asthma (vs. no)	0.068 (−0.135, 0.273)	0.506	0.064 (−0.139, 0.267)	0.533	-	-
Self-reported previous history of allergic rhinitis (vs. no)	0.045 (−0.070, 0.160)	0.441	−0.021 (−0.147, 0.105)	0.742	-	-
Wheezing (vs. no)	0.175 (0.051, 0.300)	0.006	-	-	0.131 (0.006, 0.256)	0.040
Post-COVID cough (vs. non-COVID CC)	0.165 (0.075, 0.255)	< 0.001	0.174 (0.074, 0.273)	0.001	0.154 (0.059, 0.250)	0.002

FeNO, fractional exhaled nitric oxide; 95% CI, 95% confidence interval; COVID, coronavirus disease; CC, chronic cough.
*FeNO was log-transformed for normalize the distribution.
†Model 1: adjusted for age, sex, smoking history, asthma, and allergic rhinitis.
‡Model 2: adjusted for age, sex, smoking history, and wheezing.

PROs were compared between the prospective registries (**Fig. 2**). Baseline cough severity, LCQ, and CHQ scores were comparable between post-COVID cough and non-COVID CC groups. EQ-5D-5L index was also similar, but the EQ-VAS score was significantly lower in post-COVID registry A than in non-COVID CC (62.0 ± 16.6 vs. 69.2 ± 17.3; *P* = 0.019; **Fig. 2E**).

Longitudinal follow-ups in the post-COVID cough registry

A total of 43 patients (78.2%) in post-COVID registry A underwent PRO measurement at V2. During the follow-ups, patients received usual care at the physician's discretion. Between V1 and V2 (interval: median 35 [IQR: 23–58] days), cough-specific and health PROs significantly improved, except for EQ-5D index (**Fig. 3**): (A) cough severity score from 5.3 ± 2.1 to 2.3 ± 2.1 (*P* < 0.001); (B) LCQ score from 10.8 ± 3.6 to 15.4 ± 3.7 (*P* < 0.001); (C) CHQ score from 8.4 ± 4.1 to 5.9 ± 3.6 (*P* = 0.006);and (E) EQ-VAS score from 63.2 ± 16.1 to 74.7 ± 14.0 (*P* < 0.001). The EQ-5D index increased from 0.83 ± 0.13 to 0.89 ± 0.10, albeit without a statistical

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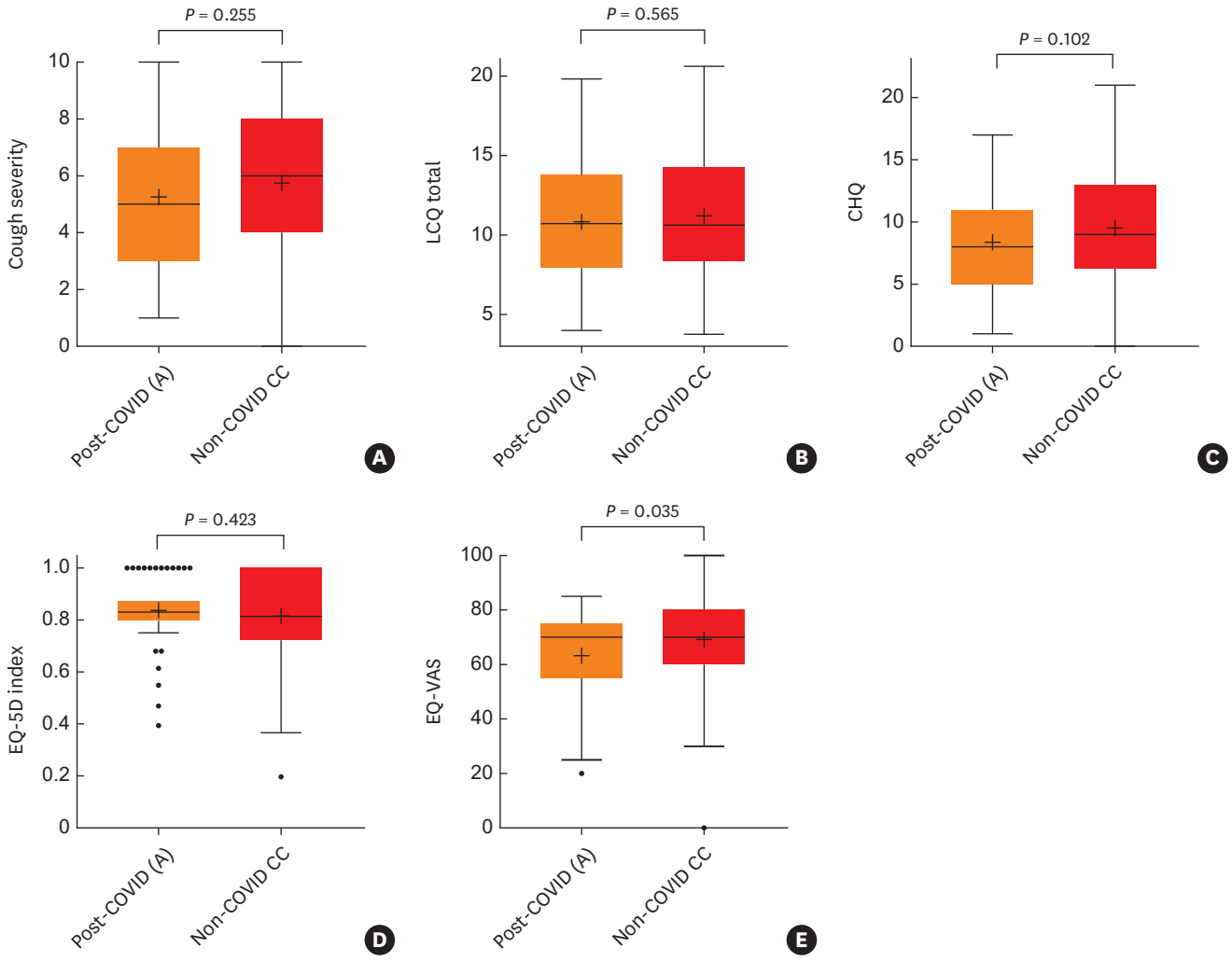

Fig. 2. Patient-reported outcomes at study enrollment. (A) Cough severity (0–10); (B) Leicester Cough Questionnaire (3–21); (C) Cough Hypersensitivity Questionnaire (0–23); (D) EQ-5D index (0–1.0); and (E) EQ-VAS score. Box indicates the lower and upper quartile; (+) sign, mean value; central line, median value; and points at the ends of the whiskers, extreme values. *P* values were determined by the Student's *t*-test.
COVID = coronavirus disease; CC, chronic cough; LCQ, Leicester Cough Questionnaire; CHQ, cough hypersensitivity questionnair; EQ-5D-5L, EuroQol five-dimensional questionnaire; EQ-VAS, EuroQol visual analogue scale.

significance in the score change ($P = 0.098$). In the LCQ score, 35 of 42 patients (83.3%) showed improvement by 1.3 or more (increase by more than the minimal important change of the scale[17]), and 3 (7.1%) had worsened (≤–1.3).

At V1, patients had median 4 (IQR: 2–7) symptoms. The most common symptom reported was sputum, followed by fatigue. At V2, the number of associated symptoms decreased to median 2 (IQR: 0–4) (**Fig. 4A**); however, several non-respiratory symptoms, such as fatigue (47.6%), sleep disturbance (21.4%), palpitation (19.0%), sore throat (16.7%), or poor oral intake (16.7%), remained frequent (>15.0%) (**Fig. 4B**).

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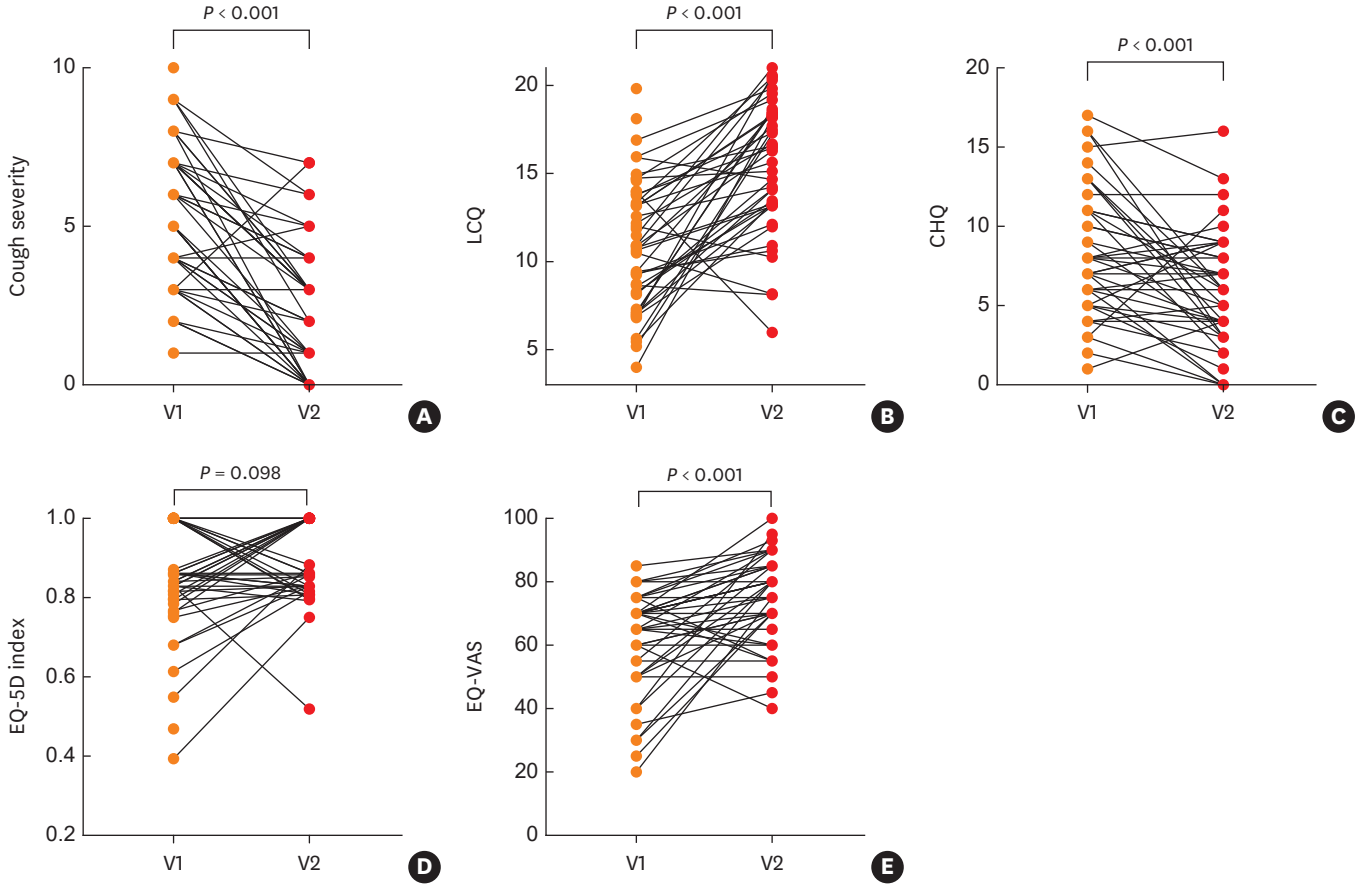

Fig. 3. Changes of patient-reported outcomes between visits 1 and 2 in the post-COVID cough registry A. *P* values were determined by paired *t*-tests. (A) Cough severity, (B) LCQ, (C) CHQ, (D) EQ-5D index, (E) EQ-VAS.
COVID = coronavirus disease; LCQ, Leicester Cough Questionnaire; CHQ, cough hypersensitivity questionnair; EQ-5D-5L, EuroQol five-dimensional questionnaire; EQ-VAS, EuroQol visual analogue scale.

DISCUSSION

The present study described the characteristics of patients with post-COVID persistent cough in the Omicron era compared to those with non-COVID CC. Most patients with post-COVID cough had a mild disease during acute infection. Their cough characteristics were comparable to those with non-COVID CC. Notably, however, FeNO elevation was more frequent in patients with post-COVID cough, and the findings were consistent in the 2 post-COVID cough registries, and the associations were consistent in multivariate analyses after adjustment for possible confounders. These suggest that T2 inflammation, or nitric oxide elevation, is clinically relevant to post-COVID persistent cough and that viral exacerbation of subclinical eosinophilic bronchitis or asthma[18] may be a frequent subset.

Despite the high social impact of post-COVID syndrome, clinical evidence and guideline recommendations for management are lacking.[5,6] In the present study, most subjects responded well to cough guideline-based usual care[9,10] as assessed by LCQ score changes. Our findings suggest that current cough guideline-based approaches can be applied in the management of post-COVID persistent cough, with special attention to identifying T2 inflammation or exhaled nitric oxide elevation. However, there were differences in patient

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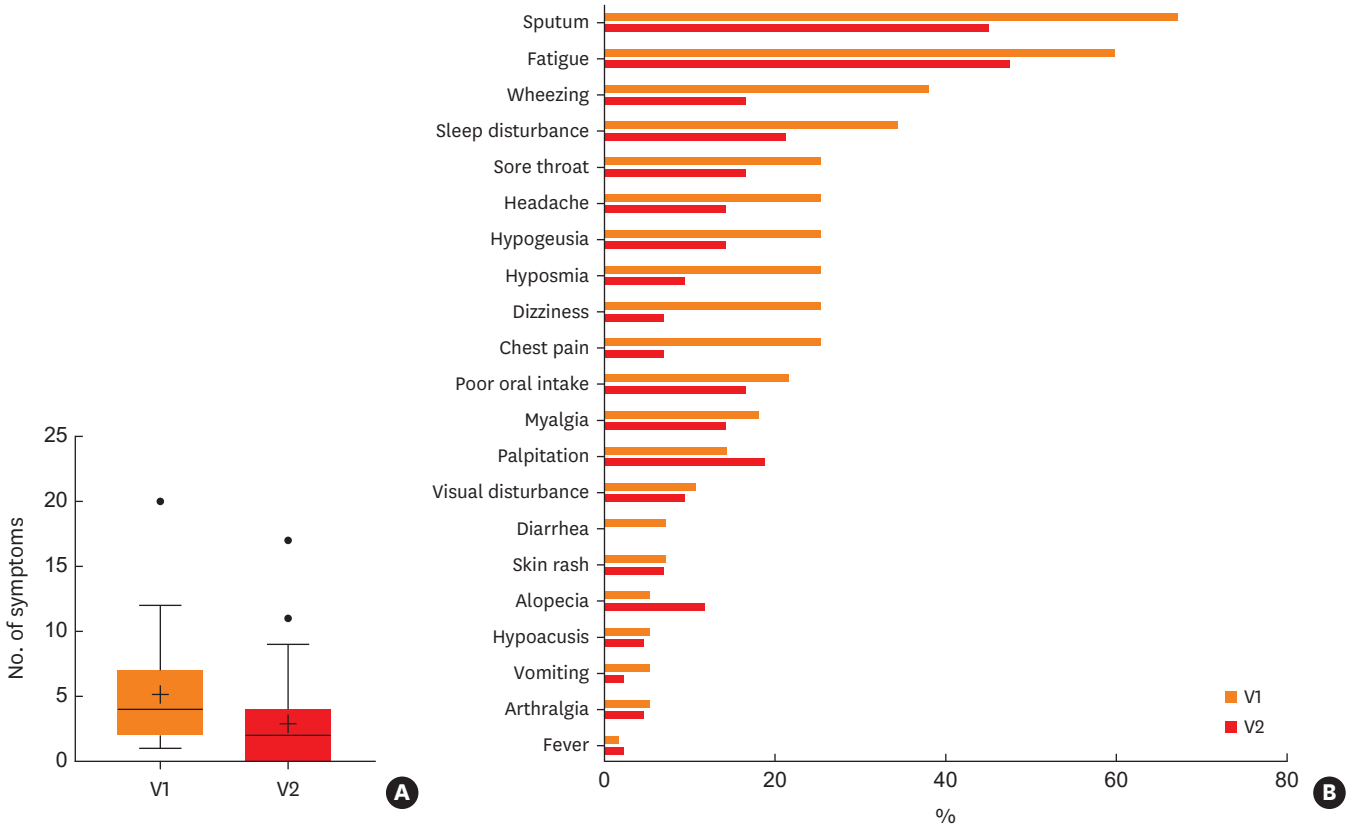

Fig. 4. General symptoms at visits 1 and 2 in the post-COVID cough registry A. (A) The number of symptoms; box indicates the lower and upper quartile; (+) sign, mean value; central line, median value; and points at the ends of the whiskers, extreme values. (B) Proportion (%) of each symptom at visits 1 and 2.
COVID = coronavirus disease.

characteristics between the 2 post-COVID registries, such as wheezing or previous history of asthma and allergic rhinitis, suggesting that post-COVID cough is a heterogeneous syndrome, like usual CC. Meanwhile, some patients did not show improvements and can be refractory to treatment.[3] Further studies are warranted to investigate patients with post-COVID treatment-refractory cough.

In the literature, there are several reports on FeNO levels in acute and post-acute COVID-19 conditions. FeNO levels were not increased during acute COVID-19 infection, but inversely correlated with disease severity, suggesting that viral infection does not cause abrupt FeNO elevation.[19-22] In the follow-up studies of patients with post-COVID pneumonia (mostly at 2–3 months after discharge), their FeNO levels were not significantly different from those of healthy controls.[23-26] Two studies reported the proportion of patients with FeNO ≥ 25 ppb (27.9% of patients with post-COVID pneumonia at 2 months[26] and 39.0% of severe COVID pneumonia survivors[27]). However, none of these studies evaluated FeNO levels in relation to cough. In addition, they were conducted before the Omicron variant epidemic. Recent reports suggest that the Omicron-associated COVID-19 during the acute stage is less severe and presents with less hyposmia/hypogeusia but more cough and sore throat compared to COVID-19 associated with the wild type or previous variants,[28] and that the incidence of long COVID is lower.[29] In this regard, our FeNO findings might be specific for post-COVID cough in the Omicron variant era.

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There are several limitations in this study. First, our study sample size was small, and the participants were recruited from referral hospitals. Thus, the findings may have limited external validity. However, we attempted to validate FeNO findings in 2 patient groups with post-COVID cough. Secondly, cough duration was longer in the non-COVID CC group (median 48 weeks) than in the post-COVID cough groups, and thus FeNO levels in patients with non-COVID CC might have been influenced by prior treatments. Thirdly, there may be residual confounding factors for FeNO levels, although we evaluated the associated factors in multivariate analyses. Fourthly, we could not evaluate the utility of FeNO levels in predicting steroid treatment responses, because multiple medications were given to patients. Fifthly, specific variants of SARS-CoV-2 infected were not confirmed in the subjects. Thus, it is not certain whether these features are specific for omicron among various variants. Omicron variants have become predominant in South Korea since February 2022.[8] We used the date of COVID-19 diagnosis to estimate the infected virus variant type and all participants were diagnosed with COVID-19 in February or later month, 2022. Finally, this study only reported a short-term clinical course. Given the nature of post-infectious cough, the cough improvements in our registry may be partly due to spontaneous resolution or regression to the mean effects. As cough can wax and wane over time, long-term follow-up studies are warranted to confirm the causes of post-COVID cough and to understand the natural history of post-COVID cough.

Despite the limitations, we believe that our brief report can lead physicians to pay attention to the assessment and management of post-COVID persistent cough.

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SUPPLEMENTARY MATERIAL

Supplementary Data S1
Materials and Methods

Click here to view

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