Original Article on Novel Insights into Chronic Cough

Risk factors contributing to impaired cough-specific quality of life at the time of admission for coronavirus disease 2019 treatment

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Background: Cough is the most common symptom of coronavirus disease 2019 (COVID-19). However, the factors contributing to impaired cough-specific quality of life (QoL) during the acute phase of COVID-19 infection remain unknown. We sought to identify such factors using the Japanese version of acute cough with the Leicester Cough Questionnaire (LCQ-acute).

Methods: Three hundred and two patients with COVID-19 admitted to Aichi Hospital between October 2020 and October 2021 completed the LCQ-acute at the time of admission. Clinical indices at the time of admission, such as presenting symptoms including cough, patient characteristics, disease severity, and biomarkers, were reviewed from the medical records. The impact of cough-specific QoL on clinical indices was assessed using two- or three-group comparisons and Pearson's correlation coefficient. Multivariate analysis was performed to determine the factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment.

Results: Two hundred and nine patients (69.2%) were coughing at the time of admission. Cough prevalence was highest, but cough-specific QoL was lowest at 8–11 days after onset. Multivariate analysis revealed that female sex, young age, gastrointestinal (GI) symptoms, and dysgeusia and/or dysosmia contributed to impaired cough-specific QoL at the time of admission for COVID-19 treatment, along with systemic and respiratory symptoms such as fever, higher C-reactive protein (CRP) levels, sputum, and dyspnea.

Conclusions: Female sex, young age, asthma, GI symptoms, dysgeusia, and/or dysosmia, along with systemic and respiratory symptoms, indicated impaired cough-specific QoL at the time of admission for COVID-19 treatment.

Keywords: Asthma; coronavirus disease 2019 (COVID-19); cough; dysgeusia and/or dysosmia; gastrointestinal symptoms (GI symptoms)

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Introduction

Cough is the most common symptom in patients seeking medical care worldwide. Most cases involve acute cough caused by viral respiratory infections (1). Although it usually resolves spontaneously within 3 weeks without specific therapy (1), the acute cough related to the common cold is associated with impaired quality of life (QoL) (2) due to the lack of specific pharmacological and non-pharmacological treatments (3). The United States Attitudes of Consumers Toward Health, Cough, and Cold survey emphasized that the cough from common cold affects the quality of sleeping, daily activity, labor productivity, and work absenteeism (4). Moreover, a post infectious cough lasting for ≥3 weeks after viral infection can further diminish the QoL (5).

The coronavirus family, together with the picornavirus family, is known as the most frequent cause of upper respiratory tract infection (URI) (6). The coronavirus disease 2019 (COVID-19) caused by severe acute syndrome coronavirus 2 (SARS-CoV-2) has been expanding worldwide since December 2019 (7). Cough is one of the most common presenting symptoms of COVID-19, along with fever and fatigue (7-9). Although cough itself does not contribute to disease severity, improvement, or mortality in COVID-19 (10,11), it is often present during hospitalization due to COVID-19 (12). Therefore, in patients with COVID-19, cough is one of the most common inconvenient symptom. However, to date, the impact of COVD-19-related acute cough on patient's QoL has not been investigated.

In this study, we sought to identify the factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment using the Japanese version of acute cough with the Leicester Cough Questionnaire (LCQ-acute). We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-358/rc).

Methods

Participants

This was a retrospective cohort study. We reviewed the medical records of 743 patients admitted to Aichi Hospital, a specialized hospital for the treatment of COVID-19, from October 15, 2020 to October 31, 2021. Patients were eligible if they completed the LCQ-acute at the time of admission. As shown in *Figure 1*, 302 of the 743 patients

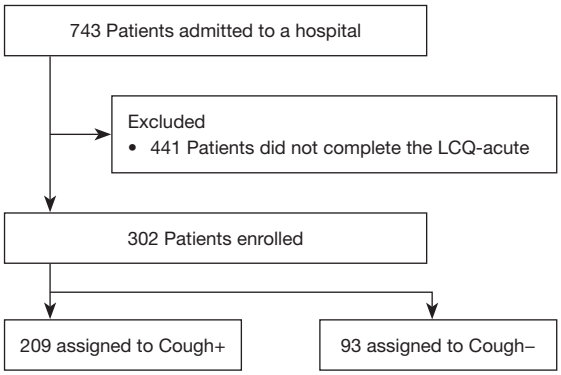

Figure 1 Flow chart of subject recruitment. LCQ-acute, acute cough with the Leicester Cough Questionnaire.

completed the LCQ acute and their data were analyzed to identify factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical board of Aichi Hospital (approval number: 2021-2). The need for written informed consent was waived by the ethical board due to the retrospective nature of this study. Instead, we posted an opt-out document regarding this study on the website of Aichi Prefectural Government to offer patients the opportunity to deny participation in the study (https://www.pref.aichi.jp/soshiki/iryo-keikaku/aichikenritsuaichibyoin.html).

Measurements

We reviewed the medical records to assess presenting symptoms and clinical findings at the time of admission due to COVID-19. Fever (defined as a body temperature ≥37.5 ℃), cough, sputum, dyspnea (at rest or on effort), fatigue, appetite loss, gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea), musculoskeletal pain, headache, dysgeusia and/or dysosmia, rhinorrhea and/or nasal congestion, and sore throat were evaluated. We also evaluated patient characteristics {sex, smoking status, body mass index (BMI), and comorbidities [asthma (including a history of asthma), chronic obstructive pulmonary disease (COPD) or emphysema, diabetes mellitus, obstructive sleep apnea, hypertension, hyperlipidemia, hyperuricemia, cardiovascular diseases, and psychological disorders]}, clinical information regarding COVID-19 (time from onset to admission, length of hospital stay, and disease severity at the time of admission), and biomarkers [white blood cells

(neutrophils, lymphocytes, monocytes, and eosinophils), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, hemoglobin A1c (HbA1c), immunoglobulin (Ig) G, IgA, IgM, procalcitonin, and D-dimer], along with the LCQ-acute score. Some information was lacking from the medical records (BMI: n=294; ferritin: n=293; HbA1c: n=281; IgG, IgA, and IgM: n=279; procalcitonin: n=286; and D-dimer: n=298). In addition, radiological findings and oxygen supplementation were used to determine disease severity.

LCQ-acute

The LCQ-acute consists of 19 items in three domains (physical, social, and psychological), and provides the patient's cough-related QoL within 24 h before admission. The total scores range from 3 to 21, with higher scores indicating better cough-specific QoL (2). The Japanese version of the LCQ-acute (13) was used in this study. Patients completed the LCQ-acute at the time of admission for COVID-19 treatment.

Disease severity

Disease severity at the time of admission was classified based on the national guidelines for COVID-19 as follows (unpublished in English. https://www.mhlw.go.jp/content/000936623.pdf): (I) mild; patients did not have pneumonia on the chest computed tomography (CT) scan without oxygen supplication, (II) moderate I; patients had pneumonia on the chest CT scan but no oxygen supplementation [saturation of percutaneous oxygen (SpO_2) ≥94% at room air], and moderate II; patients had pneumonia on the chest CT scan and hypoxia (SpO_2 ≤93% at room air). Meanwhile, our cohort did not include severe cases requiring >5 L/min of oxygen supplementation or non-invasive or invasive mechanical ventilation at the time of admission because these patients did not meet the admission criteria of Aichi Hospital, which does not have an intensive care unit.

Statistical analysis

Statistical analyses were performed using JMP version 14.3 (SAS Institute Japan, Tokyo, Japan). Values are expressed as mean (standard deviation) for continuous variables and as n (%) for categorical variables. The number of comorbidities and presenting symptoms other than cough are expressed as median (range). We performed log-transformation for non-normally distributed biomarkers, and are expressed as geometric mean (standard deviation). The primary outcome was to determine factors associated with impaired cough-specific QoL at the time of admission for COVID-19 treatment. All presenting symptoms were divided into cough positive (+) and cough negative (–) groups. Patient characteristics such as sex, BMI, smoking status, disease severity, prevalence of presenting symptoms, biomarkers, and LCQ-acute scores were compared as well between the cough (+) and cough (–) groups. The LCQ-acute scores were compared among groups according to sex, BMI, smoking status, disease severity, and all presenting symptoms using the unpaired *t*-test and analysis of variance followed by the Tukey honestly significant difference test as appropriate. The correlation between biomarkers and LCQ-acute scores was assessed using Pearson's correlation coefficient. Significant variables affecting the impaired cough-specific QoL assessed by the LCQ-acute at the time of admission for COVID-19 treatment were adopted for multivariate analysis. We arbitrarily adopted serum CRP as a biomarker of systemic inflammation in multivariate analysis because: (I) serum CRP is a sensitive and well-known biomarker of inflammation; (II) the Pearson's correlation coefficient was highest for serum CRP (R=–0.28) when compared to serum LDH, IgM and procalcitonin; (III) serum CRP levels were significantly higher in the cough (+) group than in the cough (–) group; and (IV) there was no missing serum CRP data in the present cohort. The results are presented as estimates with 95% confidence intervals (CIs) and standardized beta values. For an α error of 5%, statistical significance was set at P≤0.05.

Results

Prevalence of acute cough associated with COVID-19 at the time of admission

Patient characteristics are shown in *Table 1*. Two hundred and nine patients (69.2%) were coughing at the time of admission (*Figure 1* and *Table 1*). Patients in the cough (+) group were younger and had greater BMI, disease severity, and more presenting symptoms than those in the cough (–) group (*Table 1*). Meanwhile, there was no difference in sex, time from onset to admission, and length of hospital stay between groups. Cough-specific QoL at the time of admission due to COVID-19 was lower in the cough (+) group than in the cough (–) group (*Table 1*). When

Table 1 Patient's characteristics at the time of admission for COVID-19 treatment

Indices	All patients (n=302)	Cough (+) (n=209)	Cough (–) (n=93)	P value
Age, years	52.1 (16.1)	49.5 (14.3)	58.0 (18.1)	<0.0001
Sex (male)	191 (63.2%)	131 (62.7%)	60 (64.5%)	0.76
Time from onset to admission, days	6.8 (3.5)	6.9 (3.0)	6.4 (4.3)	0.24
The length of hospital stay, days	10.8 (5.1)	10.9 (4.4)	10.7 (6.5)	0.81
BMI, kg/m^2	24.4 (5.1)†	24.8 (5.5)‡	23.4 (3.8)§	0.02
Smoking, never/ex-/current	157 (52%)/83 (27%)/ 62 (21%)	108 (52%)/54 (26%)/ 47 (22%)	49 (53%)/29 (31%)/ 15 (16%)	0.37
Severity, mild/moderate I/moderate II	50 (16%)/156 (52%)/ 96 (32%)	27 (13%)/109 (52%)/ 73 (35%)	23 (25%)/47 (50%)/ 23 (25%)	0.02
Numbers of comorbidities	1 (0–6)	1 (0–6)	2 (0–6)	0.08
Presenting symptoms except for cough	3 (0–8)	3 (0–8)	2 (0–7)	<0.0001
Cough specific QoL (LCQ-acute) points				
Physiological	5.1 (1.1)	4.8 (1.1)	6.0 (0.6)	<0.0001
Psychological	5.1 (1.5)	4.5 (1.5)	6.2 (0.6)	<0.0001
Social	5.2 (1.7)	4.6 (1.8)	6.5 (0.6)	<0.0001
Total	15.4 (4.2)	13.9 (4.2)	18.6 (1.6)	<0.0001

Data are presented as mean (standard deviation), n (%) or median (range). +, cough symptom positive; –, cough symptom negative; †, n=294; ‡, n=205; §, n=89. COVID-19, coronavirus disease 2019; BMI, body mass index; QoL, quality of life; LCQ-acute, acute cough with the Leicester Cough Questionnaire.

arbitrarily stratified according to time from COVID-19 onset to admission, the LCQ-acute scores were lowest, and the cough prevalence was highest at 8–11 days after onset (*Figure 2A*,*2B*). Sputum, dyspnea, fatigue, appetite loss, and GI symptoms were more prevalent in the cough (+) group than in the cough (–) group (*Figure 3A*), particularly at 5–7 days after onset (*Figure 3B*). Interestingly, cough frequently presented with GI symptoms at 12–14 days after onset (*Figure 3B*). Meanwhile, the prevalence of other symptoms, including dysgeusia and/or dysosmia, was comparable between groups (*Figure 3A*).

Impact of cough-specific QoL on clinical indices during COVID-19 infection

Using the LCQ-acute, we evaluated the impact of cough-specific QoL on clinical indices at the time of admission for COVID-19 treatment stratified according to sex (male and female), age (≥50 and <50 years groups) (14), BMI (≥30 and <30 kg/m^2 groups) (15), smoking status (never, ex-smoking, and current), disease severity (mild, moderate I, and moderate II), presenting symptoms, and comorbidities (*Figure 4A*,*4B*, *Table 2*). Similar to the difference between the cough (+) and cough (–) groups, young age (<50 years), higher BMI (≥30 kg/m^2), higher disease severity, sputum, dyspnea, fatigue, appetite loss, and GI symptoms impaired cough-specific QoL at the time of admission due to COVID-19 (*Figure 4A*,*4B*). In addition, female sex, fever (temperature ≥37.5 ℃), and dysgeusia and/or dysosmia had a negative impact on QoL at the time of admission for COVID-19 treatment (*Figure 4B*).

With respect to comorbidities, patients with asthma (including six patients with a history of asthma, n=20) had significantly lower LCQ-acute scores than those without (*Table 2*). Conversely, LCQ-acute scores were significantly higher in patients with COPD, diabetes mellitus, and hyperlipidemia than in those without, respectively (*Table 2*). However, since patients with COPD, diabetes mellitus, and hyperlipidemia were significantly older than their counterparts (data not shown), we considered that the results were not affected by these three comorbidities, but by age.

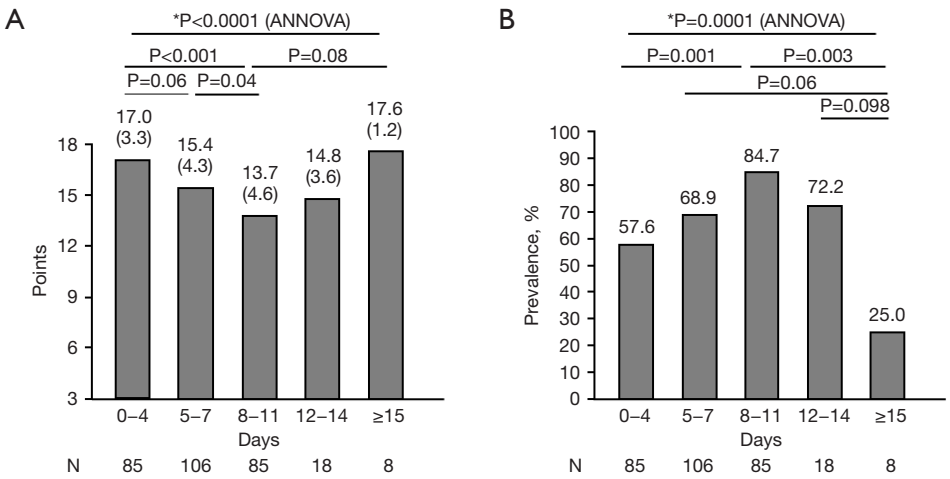

Figure 2 Association between time of disease onset to admission, cough-specific QoL (A), and cough prevalence (B). The time (days) from disease onset to admission were arbitrarily divided as follows: from 0 to 4 days (0–4, n=85), from 5 to 7 days (5–7, n=106), from 8 to 11 days (8–11, n=85), from 12 to14 days (12–14, n=18), and 15 days or later (≥15, n=8) after COVID-19 onset. LCQ-acute, acute cough with the Leicester Cough Questionnaire; QoL, quality of life; COVID-19, coronavirus disease 2019.

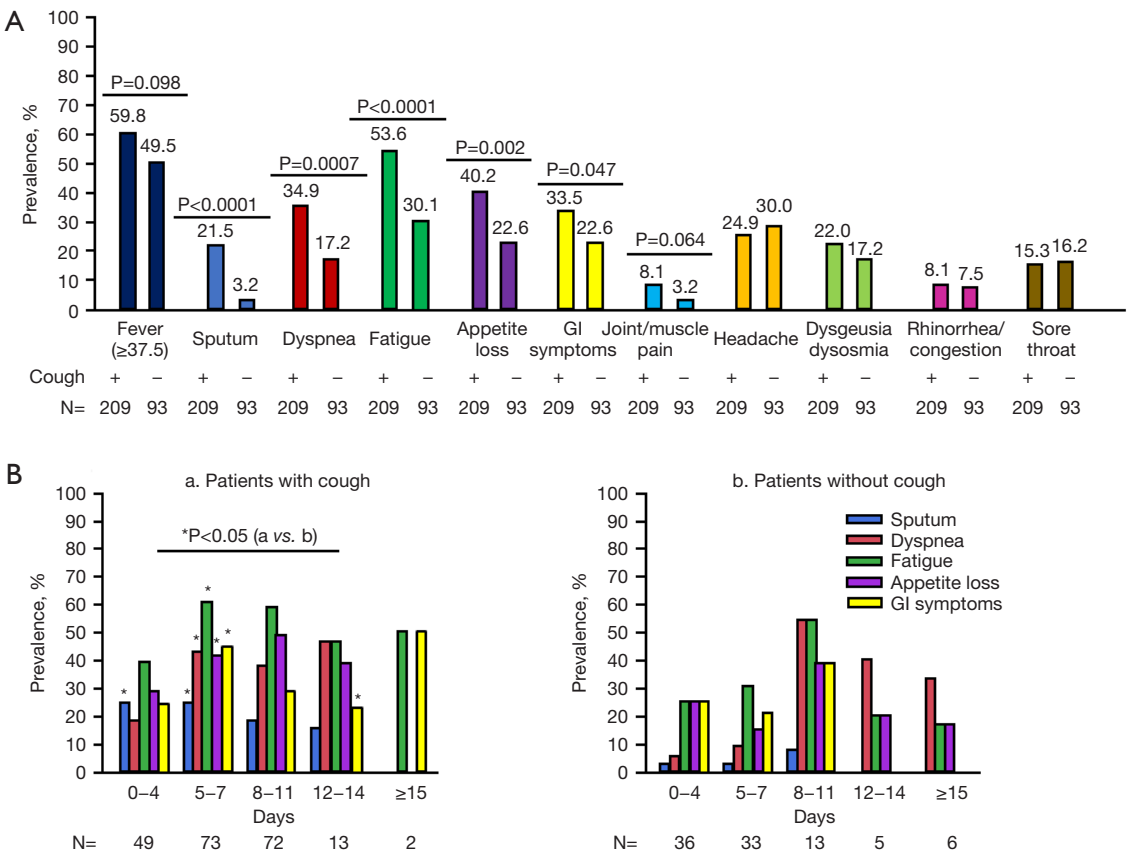

Figure 3 Prevalence of major COVID-19 symptoms (A) and time course of symptom presentation according to the presence [cough (+) group] or absence [cough (–) group] of cough (B). Significant differences in presenting symptoms (sputum, dyspnea, fatigue, appetite loss, and GI symptoms such as nausea, vomiting, and diarrhea) between the cough (+) and cough (–) groups compared from the day of disease onset to admission. +, symptoms positive; –, symptoms negative. GI symptoms, gastrointestinal symptoms; COVID-19, coronavirus disease 2019.

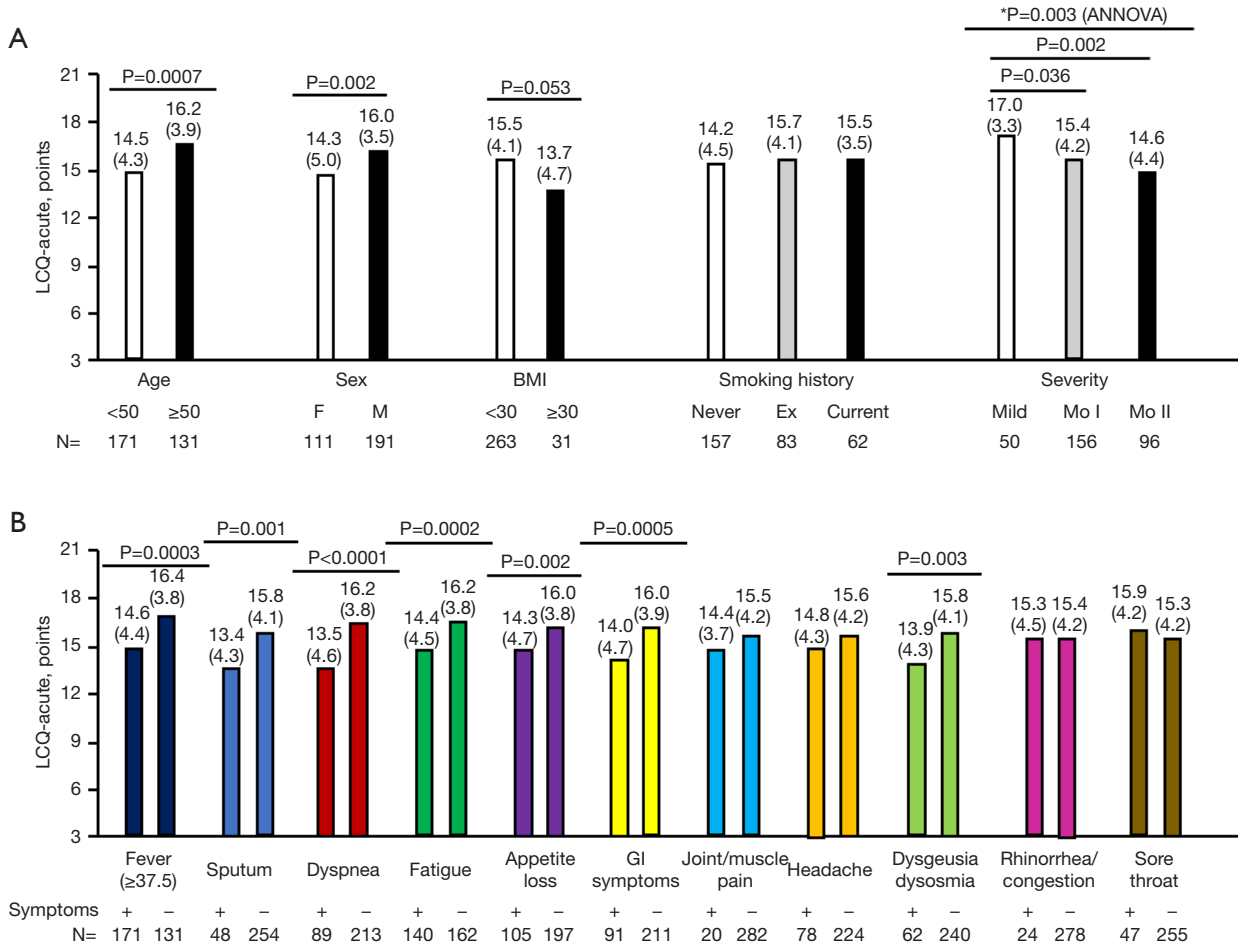

Figure 4 Differences in cough-specific QoL between 2 or 3 groups stratified by sex, BMI, smoking status, disease severity (A), and all symptoms (B). +, symptoms positive; –, symptoms negative. LCQ-acute, acute cough with the Leicester Cough Questionnaire; F, female; M, male; BMI, body mass index; Mo I, moderate I; Mo II, moderate II; GI symptoms, gastrointestinal symptoms.

Relationship between biomarkers and cough-specific QoL during COVID-19 infection

We also assessed the relationship between biomarkers and cough-specific QoL at the time of admission for COVID-19 treatment (*Table 3*). Higher serum LDH, IgM, CRP, and procalcitonin levels and lower blood eosinophil counts were significantly correlated with impaired cough-specific QoL at the time of admission for COVID-19 treatment (*Table 3*). However, all correlations were weak (*Table 3*). Additionally, serum LDH, CRP and IgM levels were significantly higher in the cough (+) group than in the cough (–) group (*Table 3*). Systemic inflammatory biomarkers were associated with impaired cough-specific QoL at the time of admission for COVID-19 treatment. On the other hand, the D-dimer plasma levels were significantly lower in the cough (+) group than in the cough (–) group. However, this difference may not be meaningful because both geometric mean values were within normal range (*Table 3*).

Risk factors contributing to impaired cough-specific QoL during COVID-19 infection

Finally, we conducted a multivariate analysis to determine the factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment (*Table 4*). The applied factors are listed in *Table 4*. We adopted serum CRP as a systemic inflammatory biomarker in multivariate analysis. Multivariate analysis revealed that young age, female sex, asthma, and dysgeusia and/or dysosmia, along with systemic and respiratory factors such as fever, higher

Table 2 Association between cough-specific QoL (total scores of the LCQ-acute) and comorbidities in patients with COVID-19

Comorbidities	(+)	(–)	P value
Asthma (including a history of asthma)	n=20	n=282	
	12.9 (4.9)	15.6 (4.1)	0.03
Allergic rhinitis/chronic rhinosinusitis	n=13	n=289	
	13.3 (4.7)	15.5 (4.2)	0.12
COPD/emphysema	n=9	n=293	
	17.3 (2.1)	15.3 (4.2)	0.02
Diabetes mellitus	n=44	n=258	
	16.7 (3.6)	15.2 (4.7)	0.01
Obstructive sleep apnea	n=8	n=294	
	14.5 (3.5)	15.4 (4.2)	0.51
Hypertension	n=80	n=222	
	15.9 (3.9)	15.2 (4.3)	0.16
Hyperlipidemia	n=52	n=250	
	16.7 (3.9)	15.1 (4.2)	0.01
Hyperuricemia	n=22	n=280	
	16.4 (3.4)	15.3 (4.3)	0.18
Cardiovascular diseases	n=17	n=285	
	17.1 (3.7)	15.3 (4.2)	0.06
Psychological disorders	n=14	n=288	
	15.2 (5.0)	15.4 (4.2)	0.91

Total LCQ-acute scores expressed as mean (standard deviation). +, comorbidities positive; –, comorbidities negative. QoL, quality of life; LCQ-acute, acute cough with the Leicester Cough Questionnaire; COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease.

CRP levels, sputum, and dyspnea, contributed to impaired cough-specific QoL at the time of admission for COVID-19 treatment (Model 1 of *Table 4*). GI symptoms in addition to young age, female sex, asthma, and dysgeusia and/or dysosmia also contributed to impaired cough-specific QoL at the time of admission for COVID-19 when the presence of pneumonia (i.e., Moderate I/II) was adopted as an applied factor instead of respiratory symptoms (Model 2 of *Table 4*). The presence of pneumonia was not related to impaired cough-specific QoL during COVID-19 infection (Model 2 in *Table 4*).

Discussion

Although this cohort consisted of patients with mild-to-moderate COVID-19 requiring hospitalization, we demonstrated for the first time that young age, female sex, asthma, GI symptoms such as nausea, vomiting, and diarrhea, and dysgeusia and/or dysosmia may impair cough-specific QoL at the time of admission for COVID-19 treatment, together with systemic condition and respiratory symptoms. Meanwhile, the presence of pneumonia with or without hypoxia was not related to impaired cough-specific QoL at the time of admission when considering only patients not requiring mechanical ventilation. Although this may indicate a stronger impact of other symptoms such as dyspnea, fever, and fatigue than that of cough in patients with pneumonia, cough might be a symptom of airway inflammation rather than lung injury. However, further researches are necessary to clarify how pneumonia affects cough-specific QoL and cough frequency in severe COVID-19 cases.

Table 3 The association of biomarkers with cough-specific QoL and cough prevalence at the time of admission for COVID-19 treatment

Biomarkers	Correlation between biomarkers and the LCQ-acute		Comparison of biomarkers between cough (+) and cough (–) groups			
	R (95% CI)	P value	All patients (n=302)	Cough (+) (n=209)	Cough (–) (n=93)	P value
WBC, /μL	–0.01 (–0.12, 0.10)	0.85	5,178 [2,219]	5,041 [1,884]	5,485 [2,819]	0.17
Neutrophils, /μL	–0.06 (–0.17, 0.06)	0.32	3,536 [2,013]	3,448 [1,723]	3,734 [2,545]	0.33
Lymphocytes, /μL	0.05 (–0.06, 0.16)	0.37	1,109 [474]	1,103 [463]	1,123 [502]	0.74
Monocytes, /μL	0.11 (–0.007, 0.22)	0.07	467 [248]	455 [236]	495 [273]	0.23
Eosinophils, /μL[¶¶¶¶]	0.16 (0.05, 0.27)	0.006	8 [7]	8 [6]	10 [7]	0.32
CRP, mg/dL[¶¶¶¶]	–0.28 (–0.37, –0.17)	<0.0001	1.9 [4.1]	2.3 [3.8]	1.3 [4.6]	0.002
LDH, IU/L	–0.20 (–0.31, –0.09)	0.0005	289 [99]	297 [101]	271 [91]	0.03
Ferritin, ng/mL[¶¶¶¶]	–0.005 (–0.12, 0.11)	0.94	325 [3][†]	328 [3][‡]	321 [3][§]	0.87
HbA1c, %	–0.02 (–0.13, 0.10)	0.78	5.8 [1.0][¶]	5.8 [1.1][††]	5.7 [0.9][‡‡]	0.42
IgG, mg/dL	0.005 (–0.11, 0.12)	0.93	1,235 [304][§§]	1,216 [305][¶¶]	1,281 [298][†††]	0.10
IgA, mg/dL	0.09 (–0.03, 0.21)	0.12	252 [110][§§]	244 [91][¶¶]	271 [144][†††]	0.12
IgM, mg/dL	–0.20 (–0.31, –0.08)	0.0008	97 [53][§§]	90 [57][¶¶]	81 [37][†††]	0.0001
Procalcitonin, ng/mL[¶¶¶¶]	–0.15 (–0.26, –0.04)	0.01	0.13 [1.6][‡‡‡]	0.13 [1.5][§§§]	0.12 [1.8][¶¶¶]	0.20
D-dimer, μg/mL[¶¶¶¶]	0.06 (–0.05, 0.17)	0.27	0.8 [2.0][††††]	0.7 [1.8][‡‡‡‡]	0.9 [2.2][§§§§]	0.02

+, cough symptom positive; –, cough symptom negative; [†], n=293; [‡], n=205; [§], n=88; [¶], n=281; [††], n=197; [‡‡], n=84; [§§], n=279; [¶¶], n=197; [†††], n=82; [‡‡‡], n=286; [§§§], n=202; [¶¶¶], n=84; [††††], n=298; [‡‡‡‡], n=208; [§§§§], n=90; [¶¶¶¶], data expressed as geometric mean [standard deviation]. Remaining data are expressed as mean [standard deviation]. QoL, quality of life; COVID-19, coronavirus disease 2019; LCQ-acute, acute cough with the Leicester Cough Questionnaire; CI, confidence interval; WBC, white blood cell counts; CRP, C-reactive protein; LDH, lactate dehydrogenase; HbA1c, hemoglobin A1c; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

Inherently, cough plays a role in preventing the aspiration of aerosolized pathogens in the airways. Indeed, impaired cough reflex sensitivity and urge-to-cough are risk factors for recurrent (16) and aspiration pneumonia (17). Meanwhile, acute viral URI can transiently increase cough reflex sensitivity; an effect maintained for 4–8 weeks after infection (18). According to previous studies, both aging and sex differences alter cough reflex sensitivity. A previous study showed significantly lower cough frequency induced by inhaled distilled water in elderly healthy subjects than in younger subjects (19). Additionally, cough reflex sensitivity is heightened in healthy women than in men (20). Accordingly, a higher transient cough reflex sensitivity during COVID-19 infection may be more common in young individuals or females.

Cough is one of the typical symptoms of asthma, along with dyspnea and wheezing (21); asthma is the most common cause of chronic cough worldwide (22). Cough in asthma is thought to be provoked not only by classical asthmatic reactions, such as airway inflammation, obstruction, and hyper-responsiveness, but also by cough reflex hypersensitivity caused by airway neuronal dysfunction (23). Acute viral URI is a trigger of asthma exacerbation which activates immune responses, including granulocyte infiltration and interferon production (24). Respiratory viruses can upregulate the expression of several receptors associated with cough induction, including transient receptor potential vanilloid 1 and ankyrin 1, on sensory nerves and airways (TRPV1 and TRPA1, respectively) (25,26). Sensory nerves in the asthmatic airways may be more easily activated by viral infection than those on normal airways. Indeed, cough reflex sensitivity to inhaled capsaicin, an agonist for TRPV1, is greater in patients with asthma than in those without (27), and is associated with poor asthma control and frequent exacerbations in patients with severe asthma (28).

GI symptoms were more prevalent not only in the early phase (5–7 days from the onset) but also in the late phase (12–14 days from the onset) of COVID-19 infection in patients presenting with cough. This suggests that GI

Table 4 Factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment

Indices	Model 1			Model 2		
	Estimates (95% CI)	P value	Standardized β	Estimates (95% CI)	P value	Standardized β
Age, years	0.03 (0.005, 0.06)	0.02	0.12	0.04 (0.009, 0.07)	0.004	0.14
Sex (female)	−1.01 (−1.45, −0.58)	<0.0001	−0.23	−1.00 (−1.45, −0.55)	<0.0001	−0.23
BMI, kg/m^2	−0.02 (−0.10, 0.07)	0.66	−0.02	−0.03 (−0.12, 0.05)	0.45	−0.04
Asthma, +	−0.93 (−1.78, −0.07)	0.03	−0.11	−1.02 (−1.88, −0.15)	0.02	−0.12
Fever (≥37.5 ℃), +	−0.45 (−0.90, −0.01)	0.045	−0.11	−0.36 (−0.81, 0.10)	0.13	−0.08
Fatigue, +	−0.27 (−0.71, 0.16)	0.22	−0.06	−0.34 (−0.79, 0.11)	0.14	−0.08
Appetite loss, +	−0.23 (−0.69, 0.23)	0.33	−0.05	−0.28 (−0.76, 0.19)	0.24	−0.06
GI symptoms, +	−0.46 (−0.93, 0.006)	0.053	−0.10	−0.57 (−1.06, −0.08)	0.02	−0.13
Dysgeusia/dysosmia, +	−0.80 (−1.231, −0.29)	0.002	−0.16	−0.72 (−1.25, −0.19)	0.008	−0.14
Log_{10} CRP, mg/dL	−1.23 (−1.97, −0.48)	0.001	−0.18	−1.64 (−2.43, −0.86)	<0.0001	−0.24
Sputum, +	−0.77 (−1.34, −0.20)	0.009	−0.14	–	–	–
Dyspnea, +	−0.90 (−1.38, −0.42)	0.0003	−0.20	–	–	–
Pneumonia, +	–	–	–	−0.18 (−0.69, 0.33)	0.49	−0.04

+, positive for asthma or symptom. QoL, quality of life; COVID-19, coronavirus disease 2019; CI, confidence interval; BMI, body mass index; GI symptoms, gastrointestinal symptoms (nausea, vomiting, and diarrhea); CRP, C-reactive protein.

symptoms may affect cough-specific QoL for a longer time than other symptoms. Both cough and GI symptoms are exacerbated by gut dysmotility and a vagally mediated reflex between the airways and the upper GI tract (29). According to an epidemiological survey on the prevalence of chronic cough in the general population in the United Kingdom, GI symptoms such as regurgitation and irritable bowel syndrome are risk factors for chronic cough (30). However, we cannot confirm whether underlying GI disorders are associated with the worsening of cough and cough-specific QoL during COVID-19 infection. Additionally, the interaction between cough and GI symptoms remains unclear as we did not evaluate whether cough was preceded by GI symptoms or not in this study.

Despite the similar prevalence of dysgeusia and/or dysosmia between patients presenting with and without cough, they contributed to impaired cough-specific QoL at the time of admission for COVID-19 treatment. Dysgeusia and/or dysosmia were predictive symptoms of SARS-CoV-2 infection, particularly when coexisting with persistent cough, fatigue, and appetite loss (31). This relationship indicates the involvement of neurogenic inflammation in the development of both cough and dysgeusia and/or dysosmia in COVID-19 by sensory neuron sensitization (32). However, there is no evidence that SARS-CoV-2 can directly infect bronchopulmonary sensory nerves and olfactory and trigeminal nerves via angiotensin-converting enzyme 2 and transmembrane serine protease 2 receptors. Further studies are necessary to elucidate the mechanism of neuro-viral interaction in SARS-CoV-2, which might help treating dysgeusia and/or dysosmia and cough during COVID-19 infection.

This study has some limitations. First, this was a retrospective, single-center, cohort study. All presenting symptoms were retrospectively reviewed from medical records. Therefore, the prevalence of all symptoms may have been underestimated. On the other hand, the LCQ-acute scores were considered reliable because the patients completed it at the time of admission. Thus, we used the cough-specific QoL, but not cough prevalence, as a primary endpoint in this study. Second, we could not evaluate the severity of symptoms. Therefore, association between cough-specific QoL and symptom severity remains unclear. Third, we did not assess the improvement in cough-specific QoL after treatment. Cough prevalence at the time of hospital discharge remains unclear. Fourth, the present results are not applicable to all patients with COVID-19 during the acute phase. In addition, we could not recruit

patients managed in the community or those with severe disease requiring mechanical ventilation. The factors contributing to impaired cough-specific QoL in the acute phase may differ depending on patient's condition. Last, we could not measure objective cough frequency using a cough monitor. The factors contributing to increased cough frequency during the acute phase of COVID-19 remain unknown. However, using a cough monitor in patients with COVID-19 was not possible to prevent infection spread.

In summary, using the LCQ-acute, we showed for the first time the factors contributing to impaired cough-specific QoL at the time of admission for COVID-19 treatment. Although most factors such as female sex, asthma, and GI symptoms were consistent with risk factors of chronic cough, dysgeusia, and/or dysosmia were also associated with impaired cough-specific QoL at the time of admission for COVID-19 treatment. The sensory nerve dysfunction triggered by SARS-CoV-2 infection might be associated with the interaction between cough and the above factors. Further studies are necessary to clarify the neuro-viral association in the pathophysiology of cough associated with COVID-19.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical board of Aichi Hospital (approval number: 2021-2). Written informed consent was waived by the ethical board owing to the retrospective nature of this study.

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