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Special Article

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Updated Clinical Practice Guidelines for the Diagnosis and Management of Long COVID

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ABSTRACT

"Long COVID" is a term used to describe a condition when the symptoms and signs associated with coronavirus disease 2019 (COVID-19) persist for more than three months among patients infected with COVID-19; this condition has been reported globally and poses a serious public health issue. Long COVID can manifest in various forms, highlighting the need for appropriate evaluation and management by experts from various fields. However, due to the lack of clear clinical definitions, knowledge of pathophysiology, diagnostic methods, and treatment protocols, it is necessary to develop the best standard clinical guidelines based on the scientific evidence reported to date. We developed this clinical guideline for diagnosing and treating long COVID by analyzing the latest research data collected from the start of the COVID-19 pandemic until June 2023, along with the consensus of expert opinions. This guideline provides recommendations for diagnosis and treatment that can be applied in clinical practice, based on a total of 32 key questions related to patients with long COVID. The evaluation of patients with long COVID should

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be comprehensive, including medical history, physical examination, blood tests, imaging studies, and functional tests. To reduce the risk of developing long COVID, vaccination and antiviral treatment during the acute phase are recommended. This guideline will be revised when there is a reasonable need for updates based on the availability of new knowledge on the diagnosis and treatment of long COVID.

Keywords: Long COVID; SARS-CoV-2; Post-COVID condition; Persistent symptoms; Management

<SUMMARY OF RECOMMENDATIONS>

1) What are the diagnostic criteria for long coronavirus disease (COVID)?

Recommendation
• Long COVID is defined as the presence of symptoms and signs persisting for more than three months after the diagnosis of coronavirus disease 2019 (COVID-19), which cannot be explained by alternative diagnoses (G, I).

2) What are the evaluation methods for long COVID patients complaining of respiratory distress?

Recommendation
• If long COVID patients complain of respiratory distress, heart and lung-related tests should be considered to evaluate the presence of cardiopulmonary diseases (B, IIa).

3) What are the evaluation methods for long COVID patients complaining of chest pain?

Recommendation
• If a patient with long COVID complains of chest pain, clinicians should consider prioritizing evaluation for the cardiovascular, respiratory, musculoskeletal, and gastrointestinal systems to exclude relevant conditions (G, IIa).

4) What are the evaluation methods for long COVID patients complaining of cough?

Recommendation
• For long COVID patients complaining of cough, evaluation should be considered based on criteria for chronic cough (B, IIa). • Simple chest X-ray and pulmonary function tests are recommended as initial tests (G, I).

5) What are the evaluation methods for long COVID patients complaining of fatigue?

Recommendation
• Medical history-taking, physical examination, blood tests, electromyography, imaging tests of the musculoskeletal system, and 6-minute walk test can exclude other organic causes that could explain fatigue. Applying fatigue scale assessment tools should be considered to evaluate the degree of fatigue symptoms (G, IIa).

6) What are the evaluation methods for long COVID patients complaining of arthralgia and myalgia?

Recommendation
• If patients with long COVID complain of arthralgia and myalgia, blood tests, imaging studies, and other evaluations may be considered to differentiate underlying causes related to the symptoms (D, IIb).

7) What are the evaluation methods for long COVID patients complaining of headaches?

Recommendation
• If a patient with long COVID complains of headaches, a neurological examination is recommended for evaluation (G, I). • If secondary headaches need to be differentiated, consideration should be given to neuroimaging studies of the brain, and it is recommended that the patient be referred to a neurologist for specialized evaluation and treatment (G, I).

8) What are the evaluation methods for long COVID patients complaining of cognitive impairment or brain fog?

Recommendation
• For cognitive impairment or brain fog (a condition characterized by difficulties with concentration and attention) in long COVID patients, it is recommended to conduct a detailed medical history, neurological examination, and neuropsychological assessment. Additionally, it is advised to discern potential underlying causes such as endocrine disorders, autoimmune diseases, infectious diseases, psychiatric conditions, sleep disorders, and medication side effects (G, I). • Brain imaging tests are recommended if brain lesions are suspected or localized neurological abnormalities are detected (G, I). • Clinicians should consider to consult a specialist with expertise in evaluating and correcting attention/concentration issues (G, IIa).

9) What are the evaluation methods for long COVID patients complaining of anxiety or depression?

Recommendation
• Immediate referral to psychiatry is recommended in cases of severe psychiatric symptoms, self-harm, or suicidal risk (G, I). • Referral to psychiatry is recommended for the exclusion of psychiatric conditions that may contribute to anxiety or depression(G, I).

10) What are the evaluation methods for long COVID patients complaining of sleep disorders?

Recommendation
• It is recommended to review sleep patterns and evaluate factors disrupting sleep conditions such as sleep apnea, restless leg syndrome, pain, and anxiety (G, I). • Clinicians should consider to consult a sleep medicine specialist for differential diagnosis of sleep disorders (G, IIa).

11) What are the evaluation methods for long COVID patients complaining of dysphagia?

Recommendation
• If a patient with long COVID complains of dysphagia, diagnostic tests, such as a video-fluoroscopic swallowing study or fiberoptic endoscopic examination of swallowing, should be considered (G, IIa).

12) What are the evaluation methods for long COVID patients complaining of olfactory or gustatory disorders?

Recommendation
• If a patient with long COVID complains of smell and taste disturbances, it is recommended to rule out other organic causes (G, I).

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13) What are the evaluation methods for long COVID patients complaining of post-exercise malaise (PEM)/post-exertional symptom exacerbation (PESE)?

Recommendation
• If a patient with long COVID complains of PEM or PESE, a questionnaire should be used to assess whether they have a movement disorder, and cardiopulmonary exercise testing may be considered as a confirmatory test (G, IIb).

14) What are the evaluation methods for long COVID patients complaining of postural tachycardia syndrome (POTS)?

Recommendation
• If a patient with long COVID complains of postural tachycardia symptoms, an active standing test (NASA Lean Test) or head-up tilt test may be considered (G, IIb).

15) How is dyspnea treated in long COVID patients?

Recommendation
• To manage dyspnea reported by patients with long COVID, adjustments in the dosage or frequency of previously used medications (*e.g.*, inhalers) may be considered, or specific treatment for newly diagnosed conditions can be initiated (C, IIb).

16) How is cough treated in long COVID patients?

Recommendation
• For the cough symptoms in patients with long COVID, empirically, antihistamines and intranasal corticosteroid use may be considered (G, IIb).

17) How is fatigue treated in long COVID patients?

Recommendation
• For fatigue symptoms in patients with long COVID, correctional therapy of the underlying causes is necessary. If no specific underlying causes exist, rehabilitation therapy may be considered (G, IIb).

18) How is arthralgia or myalgia treated in long COVID patients?

Recommendation
• For treating joint and muscle pain in patients with long COVID, referral to a related specialist may be considered (D, IIb).

19) How is headache treated in long COVID patients?

Recommendation
• After excluding secondary headaches, symptomatic treatment is provided for primary headaches. In particular, if migraine-like symptoms persist and interfere with daily life, preventive treatment for migraines should be considered (G, IIa).

20) How are cognitive impairments or brain fog (reduced concentration and attention) treated in long COVID patients?

Recommendation
• Patients who are found to have objective symptoms of cognitive impairment during cognitive screening are recommended to be referred to a specialist for further evaluation and treatment (G, I). • If there are suspected causes that may induce cognitive impairment or brain fog (decreased concentration/attention) symptoms, such as medication side effects, neurological disorders, endocrine disorders, autoimmune or infectious diseases, mood disorders, or sleep disorders, clinicians should consider to consult relevant specialists (G, IIa).

21) How are anxiety or depressive symptoms treated in long COVID patients?

Recommendation
• If there are severe psychiatric symptoms or a risk of self-harm or suicide, immediate psychiatric consultation is recommended (G, I). • Referral to a psychiatrist is recommended for the purpose of ruling out psychiatric conditions that may explain anxiety or depression (G, I). • When a patient with long COVID exhibits depressive symptoms, the prescription of selective serotonin reuptake inhibitors may be considered (C, IIb).

22) How are sleep disorders treated in long COVID patients?

Recommendation
• If there is a sleep disorder, it is recommended to eliminate factors that disturb sleep (habits, use of substances, the environment, etc.) and identify and address causative conditions (such as sleep apnea, restless legs syndrome, pain, anxiety, etc.) (G, I). • Clinicians should consider to refer to a sleep medicine specialist (G, IIa). • Clinicians should consider to treat patients with cognitive-behavioral therapy, pharmacotherapy, and sleep diaries (G, IIa).

23) How is dysphagia treated in long COVID patients?

Recommendation
• As for the dysphagia associated with long COVID, clinicians should consider swallowing rehabilitation exercises, neuromuscular electrical stimulation therapy, and improving the nutritional status for the patients (G, IIa).

24) How are olfactory and gustatory disorders treated in long COVID patients?

Recommendation
• For patients with long COVID, olfactory training is recommended to improve olfactory dysfunction (A, I). • For patients with long COVID, topical corticosteroid nasal sprays may be considered to improve olfactory dysfunction (A, IIb).

25) How are PEM or PESE treated in long COVID patients?

Recommendation
• In cases where there is discomfort after exercise in patients with long COVID, educating on the importance of alternating between appropriate activity and rest may be helpful (G, IIb).

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26) How is POTS treated in long COVID patients?

Recommendation
• When patients with long COVID complain of POTS symptoms, non-pharmacological and pharmacological treatments may be considered depending on their hemodynamic status (G, IIb).

27) Should prophylactic anticoagulants be used to long COVID patients?

Recommendation
• The use of anticoagulants or antiplatelet drugs for the purpose of preventing blood clots is not recommended (C, III). • However, if a blood clot is diagnosed, treatment with anticoagulants or antiplatelet drugs is recommended according to the relevant guidelines (A, I).

28) Is the administration of systemic steroids helpful for long COVID patients?

Recommendation
• If there are no other conditions necessitating steroid use in patients with long COVID, the administration of systemic steroid is not recommended (D, III).

29) Is the administration of anti-fibrotic drugs necessary in long COVID patients?

Recommendation
• If pulmonary fibrosis is suspected in patients with long COVID, chest computed tomography is recommended to assess the degree of pulmonary fibrosis (A, I). • The use of antifibrotic drugs is not recommended without confirming the degree of pulmonary fibrosis (G, III).

30) Is respiratory rehabilitation therapy necessary for long COVID patients?

Recommendation
• Respiratory rehabilitation therapy is recommended for patients with long COVID, considering underlying lung conditions, the need for intensive care unit treatment, the presence of comorbidities (neurological and muscular disorders), and other relevant factors (A, I).

31) Can antiviral therapy for the treatment of COVID-19 reduce the risk of developing long COVID?

Recommendation
• Antiviral therapy is recommended in the early stages of severe acute respiratory syndrome coronavirus 2 infection to prevent long COVID (A, I).

32) Can vaccination to prevent COVID-19 reduce the risk of developing long COVID?

Recommendation
• COVID-19 vaccination is recommended to prevent long COVID (A, I).

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1. BACKGROUND AND PURPOSE OF THE GUIDELINE

As of February 2024, more than 700 million individuals have been confirmed with coronavirus disease 2019 (COVID-19). Most patients diagnosed with COVID-19 experience mild symptoms and recover within a few weeks. However, some continue to experience various health issues for an extended period even after the initial infection. Long COVID refers to a condition whereby some individuals with COVID-19 continue to experience a series of symptoms several months after acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These symptoms vary and can affect multiple organ systems. However, the exact mechanism behind the occurrence of prolonged symptoms following COVID-19 is not yet fully understood, and there is currently no consensus among various academic societies and institutions regarding the diagnostic criteria. Furthermore, due to the lack of medical evidence regarding which tests and treatments are appropriate for its various symptoms, clinical decisions are ultimately made based on individual clinicians' empirical judgment. In response, the Korean Society of Infectious Diseases (KSID) deemed it necessary to develop clinical guidelines based on the medical judgment of experts in the field and the latest evidence. Therefore, on September 21, 2022, KSID released the "Preliminary Guidelines for the Management of long COVID." However, at the time of the drafting of the preliminary guidelines, there was a significant lack of medical research on long COVID, making it difficult to conduct a systematic review of the literature on its diagnosis and treatment. Therefore, the guideline was not evidence-based but practical and rapidly developed, based on the available evidence and expert judgments. Therefore, at present, over a year since the publication of the preliminary guideline, it has been deemed necessary to develop an updated evidence-based guidelines for long COVID by integrating various additional research findings through a systematic review of the literature. Hence this revised guidelines for the management of long COVID.

This guideline includes basic principles for diagnosing and treating patients with long COVID. This guideline has been systematically developed to assist decision making by clinicians and patients with long COVID on the appropriate medical care for specific clinical situations. Therefore, this guideline may serve as a reference for clinicians treating patients with long COVID, and it can be utilized to assess the appropriateness of their final judgment, considering the various presentations of each patient. Furthermore, the present guideline can be utilized for clinical and educational purposes by individuals but not for commercial or medical review purposes. Anyone wishing to use it for purposes other than for medical treatment and education must submit a written request to the drafting committee to obtain a written approval.

2. METHODS

(1) Composition of the guidelines development committee

In February 2023, as part of the Korea Disease Control and Prevention Agency's COVID-19 sequelae research project, the long COVID Treatment Guideline Steering Committee of the KSID was constituted. The clinical practice guideline working committee consisted of 13 specialists from infectious diseases, respiratory medicine, cardiology, neurology, and psychiatry specialties.

(2) Process of developing the guidelines

Currently, major countries and organizations have published many practice guidelines related to long COVID. Those existing guidelines on long COVID were adapted to develop the present guideline. The results of any recent studies were also added as evidence.

1) Search sources

The sources for the comprehensive literature search included PubMed, EMBASE, Cochrane CDSR, and KMBASE databases. Additionally, manual searches were conducted to supplement any missing studies. Preprint databases (MedRxiv, etc.) were excluded from the search source.

2) Search strategy

A search strategy was developed primarily using PubMed, reflecting search terms suggested by the committee members, considering the questions about and symptoms of long COVID. Preliminary search results were discussed to incorporate additional feedback and suggestions. The search terms included terms related to long COVID, such as "long COVID," "post COVID," and "after COVID"; each linked to specific symptoms for the search process. Once the final search strategy was confirmed, the search was conducted across all selected databases from January 2020 to February 2024.

3) Literature selection criteria

Inclusion and exclusion criteria were established for each

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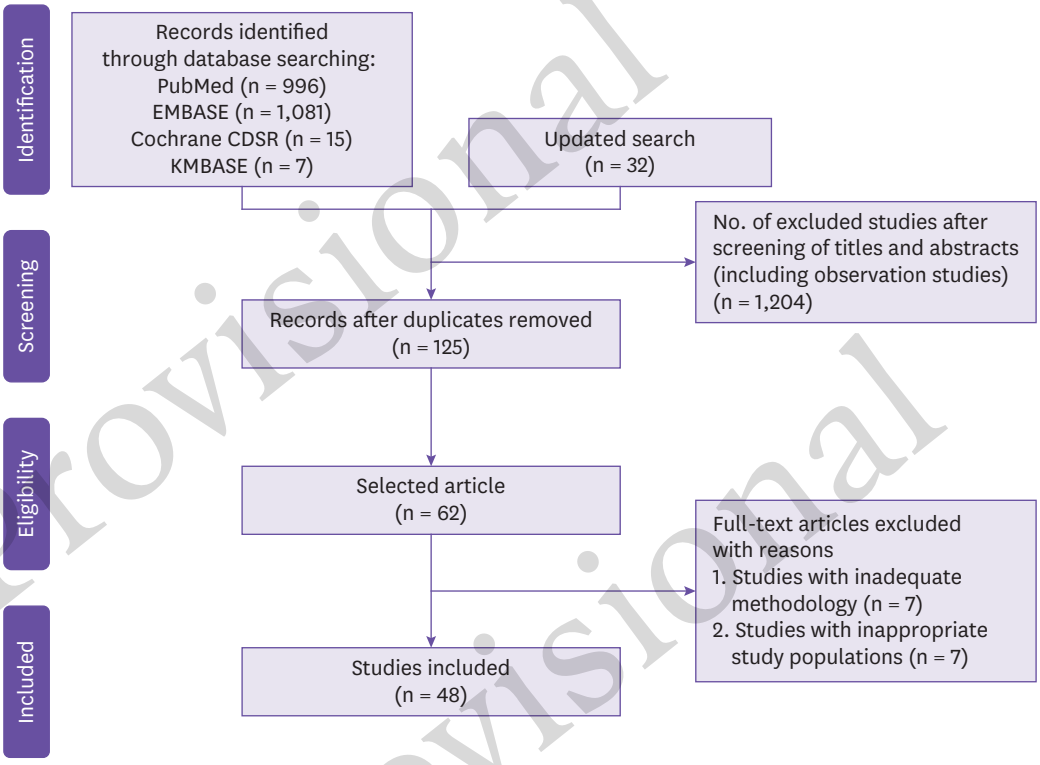
PubMed
#1: COVID-19 OR "COVID 19" [MeSH Terms] OR COVID-2019 OR SARS-CoV-2 OR 2019-nCoV OR 2019-SARS-CoV-2: 30,437 studies
#2: survivor* OR recover* OR persistent OR follow up OR discharge* OR sequela* OR long COVID: 345,847 studies
#3: ("long term" AND follow up) OR 1 year OR one year OR 12 months OR twelve months OR after OR post: 208,575 studies
#4: ((long COVID) OR (post covid)) OR (after covid)) AND ("antiviral"[All Fields]): 797 studies
#5: #1 AND #2 AND #3 AND #4
Filters: Abstract, Clinical Trial, Clinical Trial, Phase IV, Guideline, Meta-Analysis, Observational Study, Randomized Controlled Trial, Review, Systematic Review, Humans, English, from 2020 to 2023: 996 studies

[PRISMA Flow chart for study selection process in developing guideline]



clinical question based on the Population, Intervention, Comparison and Outcomes methods and study design. The criteria were developed following discussions by the Working Committee. The criteria included: 1) clinical studies reporting on the number of patients with clinical characteristics of long COVID, 2) studies in which the MeSH terms or keywords were presented for methodology, and 3) studies written in English. The exclusion criteria were: 1) case reports, 2) studies without statistical tables, and 3) gray literature (conference presentations, dissertations, hypothesis papers, etc.).

4) Assessment of risk of bias of selected literature
To assess the quality of the studies selected finally, appropriate instruments according to the study design were utilized. In this process, each study was independently evaluated by two or more researchers, and in case of disagreement, decisions were made based on expert consultation.

- **Quality appraisal tool for assessing the guidelines: Appraisal of Guidelines Research and Evaluation II (AGREE 2) (see Supplemental materials)**

The AGREE tool is the most widely used clinical practice guideline evaluation tool internationally. It is used to calculate scores for each of the following six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of expression, applicability, and

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editorial independence. These domains are independent of each other and should not be combined into a single quality indicator score. At least two evaluators are required to evaluate each item on a 7-point scale.

- **Systematic reviews and meta-analysis quality assessment tools: the Scottish Intercollegiate Guidelines Network (SIGN)**

The SIGN checklist includes 10 questions covering research question, randomization, allocation concealment, blinding, baseline similarity, intention-to-treat analysis, outcome reporting, dropout rates, and institution and individual homogeneity, aiming to evaluate the quality of individual randomized controlled trials (RCTs).

- **Quality assessment tools for RCTs: the Joanna Briggs Institute (JBI) checklist**

The JBI checklist for analytical cross-sectional studies consists of eight items covering section criteria for subjects, description of selection criteria, exposure status for disease risk, disease diagnosis, control of confounding variables, measurement of outcome variables, and appropriateness of statistical analysis methods. For each item, 'yes' was rated 1 point, and 'unclear,' 'no,' and 'not applicable' were 0 points.

5) Level of evidence and recommendation

The literature (or guidelines) used as the basis for the draft recommendations were classified into four levels of evidence by the Working Committee using the following criteria (**Table 1**):

The recommendations were graded based on the modified Grading of Recommendations Assessment, Development, and Evaluation. The Working Committee classified the recommendation grades using a method that comprehensively reflects factors such as the level of evidence, benefits and harms, and applicability in clinical practice (**Table 2**). The recommendation grades have been adjusted upward by the drafting and writing committees for recommendations with benefits or high utility in clinical settings based on a user survey despite the low level of evidence.

(3) Development according to evidence-based consensus

This guideline applied an adaptation method based on the existing KSID guidelines. To update the evidence, all panel members were provided with literature searched in electronic document forms. The panel members were also assigned key questions on overview, diagnosis, treatment, and prevention related to 14 specific clinical symptoms; each member then drafted recommendations for the questions assigned. The panel members shared and reviewed their thoughts on the guidelines recommended by each panel member through electronic means, video conferences, and direct discussions, and finalized the guidelines. All panel members approved the final guidelines, and feedbacks were obtained from external peer review, which was reviewed by the entire panel who made changes, when necessary.

Table 1. Level of evidence

Level of evidence	Definition
A	Evidence for recommendations is clear There is at least one randomized controlled trial (RCT), meta-analysis, or systematic reviews
B	Evidence for recommendations is reliable. There is at least one well-conducted non-RCT, such as a patient-control study or cohort study.
C	There is evidence for recommendations but not reliable Only low-level evidence is available, such as observational studies and case reports.
D	The recommendations are based on expert opinion derived from clinical experience and expertise.
G	Evidence for recommendations is from high-quality clinical practice guidelines.

Table 2. Recommendation grades

Recommendation grades	Definition	Notation of recommendation
Class I	The level of evidence (Grade A) and benefits are clear, with high utility in clinical settings	Recommended
Class IIa	The level of evidence (Grade B) and benefits are credible, with high or moderate utility in clinical settings	Should be considered
Class IIb	The level of evidence (Grade C or D) and benefits are not credible, yet with high or moderate utility in clinical settings	May be considered
Class III	The level of evidence (Grade C or D) is not credible, and there is a risk of adverse outcomes, with low utility in clinical settings	Not recommended

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3. OVERVIEW

(1) What is the definition of long COVID?

The symptoms/signs of COVID-19 persist for up to 4 weeks from diagnosis; this is referred to as acute COVID-19 (acute SARS-CoV-2 infection). The definition of long COVID, commonly referred to as post-COVID-19 syndrome, slightly varies across different institutions or guidelines. However, generally, it follows the definition provided by the World Health Organization (WHO), which defines post-COVID-19 conditions as symptoms/signs that occur during or after acute COVID-19 that cannot be explained by other diagnoses and persist for at least 3 months following diagnosis [1]. Other alternative terms include long COVID, long-haul COVID, chronic COVID, post-COVID-19 conditions, post-COVID-19 syndrome, and post-acute sequelae of SARS-CoV-2 infection (PASC). According to the National Institute for Health and Clinical Excellence (NICE) guidelines in the United Kingdom (UK), symptoms/signs persisting and improving within 4 weeks to 3 months after diagnosis of acute COVID-19 or thereafter are referred to as "ongoing symptomatic COVID-19," while "post-COVID-19 syndrome" is a term used to describe symptoms persisting beyond 3 months [2]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines define long COVID as symptoms persisting beyond 3 months following COVID-19 diagnosis, with no alternative diagnosis explaining the symptoms [3]. In contrast, the National Institutes of Health (NIH) in the United States refer to symptoms persisting beyond 4 weeks following COVID-19 diagnosis as "PASC" [4]. Although there is insufficient evidence for specific pathophysiological changes in the 3 months following the onset of COVID-19, there remains a need for standardized terminology for research and clinical trials on post-COVID-19 conditions. Therefore, in this guideline, the term post-acute COVID-19 is defined as one or more symptoms/signs that occur during or after acute COVID-19 within 4 weeks to 3 months from the diagnosis and cannot be explained by other conditions, while the term long COVID describes symptoms that persist beyond 3 months [5].

(2) What are the epidemiology and risk factors of long COVID?

Based on previous findings, if a conservative estimate of the prevalence of long COVID is applied at 10%, then a minimum of over 65 million individuals worldwide may have experienced long COVID. There are regional variations, with higher prevalence rates observed in Asian than Europe and North America [6]. The estimated prevalence rates are 10 - 30% in non-hospitalized patients, 50 - 70% in hospitalized patients, and 10% - 12% in vaccinated individuals. Long COVID can occur in individuals of all age groups, and while severity during acute COVID-19 may be associated with its occurrence, it can also occur in patients with mild COVID-19. The diagnosis rate is highest among individuals aged 36 - 50 years, and most cases of long COVID are known to occur in not-hospitalized patients with mild SARS-CoV-2 infection [7]. When comparing the incidence rates by variant, the rate of long COVID occurrence is relatively lower following infection with the Omicron variant, at 4.5%, compared with the 10.8% following infection with the Delta variant [8]. In other studies, the incidence rate of long COVID following infection with the Omicron variant, according to the WHO definition criteria, was estimated at 11% [9]. Generally, symptoms improve over time [3], however, a meta-analysis including over 1.28 million survivors from two countries revealed that within 12 months of infection, 49% of patients had at least one symptom of long COVID [10]. A domestic observational study tracking patients with long COVID reported that 48.8% - 52.7% of patients exhibited long COVID symptoms 12 months post-infection [11, 12]. The average duration of long COVID in patients who did not receive hospital treatment was 4 months, while that of patients who received hospital treatment was 9 months [13].

Risk factors associated with the occurrence of long COVID include being female, older age, high body mass index, smoking history, underlying conditions (such as anxiety or depression, asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease), past hospitalization (or admission to the intensive care unit). However, previous studies have reported various symptoms associated with long COVID [14]. Two consistent risk factors associated with long COVID are sex and the severity of acute COVID-19 illness. Females are at twofold higher risk of developing long COVID than males [3], and are at higher risk of developing long COVID accompanied by neurological/psychiatric symptoms [15, 16]. Additionally, severe illness during acute COVID-19 is strongly associated with fatigue [3]. One of the prominent factors known to reduce the occurrence of long COVID is vaccination. Indeed, receiving two doses of the vaccine lowers the risk of developing long COVID [14]. However, the risk of developing neurological, psychiatric, musculoskeletal, and respiratory long COVID symptoms increases with each subsequent reinfection, occurring two or three times, even in individuals who received two or more doses of COVID-19 vaccine [17].

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(3) What are the clinical features and pathophysiology of long COVID?

After acute SARS-CoV-2 infection, most patients show symptom improvement, however, approximately 15% of patients, including those with severe illness, may experience clinical sequelae following chronic organ damage or present symptoms of long COVID [18]. Long COVID can newly begin after recovery from acute SARS-CoV-2 infection symptoms, persist from acute symptoms, or evolve and recur over time [1]. While the time taken to recover from acute SARS-CoV-2 infection varies among individuals, most show improvement by around three months [3]. And, long COVID is associated with a decrease in quality of life [11, 15], and the lack of specific diagnostic tests and effective treatments remains to be addressed. According to the United States' Centers for Disease Control and Prevention (CDC), symptoms/signs following COVID-19 can persist in approximately one out of every five individuals aged 18 - 64 years and one out of every four aged ≥65 years. These symptoms/signs can manifest in numerous ways, including, but not limited to, fever, shortness of breath, cough, chest pain, palpitations, dizziness, abdominal pain, diarrhea, headache, dizziness, sensory abnormalities, loss of smell, loss of taste, pain, fatigue, post-exercise malaise (PEM)/post-exertional symptom exacerbation (PESE), joint pain, muscle pain, cognitive impairment, insomnia, depression/anxiety, post-traumatic stress disorder (PTSD), menstrual irregularities, erectile dysfunction, hair loss, and thirst. The pathophysiological mechanisms underlying long COVID are described as immune dysregulation due to the persistent presence of the SARS-CoV-2 or reactivation of other viruses such as Epstein-Barr virus (EBV) or human herpesvirus 6, microbiota dysbiosis, autoimmunity, blood clotting and endothelial abnormalities, and dysfunctional neurological signaling [7].

A previous study that tracked 9,764 individuals, both SARS-CoV-2-infected and uninfected, who participated in the Researching COVID to Enhance Recovery adult cohort study in the United States for up to 6 months following acute SARS-CoV-2 infection, reported the following prevalent long COVID related symptoms: post-exertional malaise (87%), fatigue (85%), brain fog (64%), dizziness (62%), gastrointestinal symptoms (59%), and palpitations (57%) [19]. Brain fog symptoms include decreased concentration, memory impairment, and cognitive dysfunction. Upon evaluating the frequency of long COVID syndrome up to two years following SARS-CoV-2 infection among patients in South Korea, previous studies confirmed that neurological and psychiatric symptoms such as fatigue (34.8%), memory impairment (30.3%), difficulty concentrating (24.2%), insomnia (20.5%), and depression (19.7%) persisted for longer periods at higher frequencies than other symptoms. A comparative study between hospitalized and non-hospitalized patients up to two years following SARS-CoV-2 infection found that 59.7% of hospitalized patients and 67.5% of non-hospitalized patients may experience at least one long COVID-related symptom. However, the authors observed no significant difference in the frequency of long COVID symptoms between hospitalized and non-hospitalized patients [20]. Memory impairment was higher in the hospitalized group (20%) than non-hospitalized group (15.9%); however, no significant difference in the frequency was observed between the two groups [21]. After infection with the Omicron variant, memory impairment was observed in 28% of cases, while decreased concentration was observed in 20% [9].

In particular, among long COVID symptoms observed in Omicron-infected patients with a median age of 34 years, memory impairment was observed in 1.3% of cases [22]. A biobank study comparing brain imaging changes before and after infection in the UK reported reductions in brain parenchymal volume, tissue damage, and cognitive impairment [23]. Therefore, continuous monitoring for degenerative neurological disorders, such as early-onset dementia, is necessary.

4. DIAGNOSIS

(1) What are the diagnostic criteria for long COVID?

Recommendation
• Long COVID is defined as the presence of symptoms and signs persisting for more than three months after the diagnosis of COVID-19, which cannot be explained by alternative diagnoses (G, I).

Long COVID is defined based on the duration of symptoms persisting following diagnosis of COVID-19. The CDC, the NIH, NICE, and ESCMID have variously defined long COVID as the persistence of symptoms or signs for 4 weeks to 3 months following acute SARS-CoV-2 infection [2-4]. The WHO defines post-COVID-19 condition as the occurrence of symptoms or signs during or after acute COVID-19, persisting for a minimum of 2 months and extending beyond 3 months from the onset of acute COVID-19, with

no alternative diagnosis explaining the symptoms or signs [1, 24]. The WHO Delphi consensus did not achieve terminological standardization for the various post-COVID-19 conditions (COVID-19 syndrome, post-acute COVID-19, and PASC); however, the current guidelines use the term "long COVID" to refer to these conditions [1]. In this clinical guideline, long COVID is defined as the presence of symptoms and signs persisting for more than 3 months after the diagnosis of acute SARS-CoV-2 infection that cannot be explained by alternative diagnoses.

(2) What various diagnostic tests can be conducted based on the clinical characteristics of patients with long COVID?

1) What are the evaluation methods for long COVID patients complaining of respiratory distress?

Recommendation
• If long COVID patients complain of respiratory distress, heart and lung-related tests should be considered to evaluate the presence of cardiopulmonary diseases (B, IIa).

A systematic literature review and meta-analysis on chronic respiratory distress following COVID-19 revealed that 26 - 41% of patients reported respiratory distress. This symptom significantly decreased between 1 - 6 and 7 - 12 months post-infection. Respiratory distress was more common in severe/critical infections upon hospitalization and among females, with fewer reports in patients from Asia compared with Europe or North America [25]. In multidisciplinary clinical guidelines and treatment guidelines for post-COVID-19 cardiac complications in the United States, patients with persistent respiratory distress are recommended to undergo echocardiography and testing for B-type natriuretic peptide (BNP) or N-terminal-pro-BNP (NTpro-BNP) to differentiate cardiac conditions [26]. Also, multicenter, prospective observational studies have suggested that simple chest X-rays and computed tomography (CT) scans may have a low correlation with respiratory distress symptoms; however, it is necessary for differentiating other parenchymal lung diseases and pulmonary fibrosis. Results of pulmonary function tests including lung diffusion capacity, the 6-minute walk test (6MWT), and cardiopulmonary exercise testing (CPET) may be associated with respiratory distress and related to the initial severity [26, 27]. A meta-analysis of nine studies (a total of 823 individuals) on cardiopulmonary exercise testing found that in patients with persistent long COVID symptoms, the mean peak oxygen consumption was 4.9 mL/kg/min lower than those without long COVID symptoms [28]. While the sample size of the subjects was small, hence the reliability was low, it was suggested that CPET could be useful in distinguishing exercise-induced dyspnea. To date, systematic literature reviews and meta-analysis specifically evaluating the assessment of chronic dyspnea following COVID-19 are lacking. Various guidelines provide diverse recommendations for the evaluation of dyspnea. Evaluations should be considered according to expert recommendations, which may change or be supplemented as new evidence emerges.

2) What are the evaluation methods for long COVID patients complaining of chest pain?

Recommendation
• If a patient with long COVID complains of chest pain, clinicians should consider prioritizing evaluation for the cardiovascular, respiratory, musculoskeletal, and gastrointestinal systems to exclude relevant conditions (G, IIa).

Persistent chest pain can occur in 10 - 20% of patients 30 - 60 days following acute SARS-CoV-2 infection [29]. Chest pain occurring in patients more than 3 months after acute SARS-CoV-2 infection should first be evaluated to discern the possibility of abnormalities and inflammatory responses in the cardiovascular system, respiratory system, musculoskeletal system, and gastrointestinal system. Patients who have not undergone evaluation to determine the cause of chest pain following COVID-19 diagnosis should be assessed according to the guidelines for routine chest pain evaluation [30, 31]. In patients with persistent chest pain, electrocardiography, serum troponin, and echocardiography may be performed to confirm or exclude myocardial injury [31, 32]. However, in patients with concurrent myocarditis following COVID-19 diagnosis, the time required for serum troponin levels to normalize remains to be determined. Therefore, a single elevated troponin measurement may not necessarily indicate cardiac disease. Echocardiography can be used to assess abnormalities in the myocardium and pericardium in patients with persistent symptoms. It may also be used as a follow-up test in patients with myocarditis, pericarditis, or heart failure during the acute phase, typically 2 - 3 months following diagnosis, for follow-ups [3]. According to one study, the frequency of myocarditis occurrence following COVID-19 diagnosis was 0.21 cases per 1,000 individuals in a mean follow-up of 9.5 months, which was higher than

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that in patients without a history of COVID-19 (0.09 cases per 1,000 individuals) [33]. If a patient complains of chest pain and shows abnormalities on basic tests, conducting cardiac magnetic resonance imaging (MRI) may be considered to assess the possibility of post-acute COVID-19 myocarditis [31].

3) What are the evaluation methods for long COVID patients complaining of cough?

Recommendation
• For long COVID patients complaining of cough, evaluation should be considered based on criteria for chronic cough (B, IIa). • Simple chest X-ray and pulmonary function tests are recommended as initial tests (G, I).

When patients hospitalized for acute SARS-CoV-2 infection were followed up for 6 weeks to 6 months, the prevalence of persistent cough was 18% (95% confidence interval [CI], 12 - 24%; I^2 = 93%). However, the prevalence varied based on the characteristics of the study population, treatment, and duration of follow-up. The cause of persistent cough after acute SARS-CoV-2 infection remains to be fully understood; however, it may be associated with chronic fatigue, respiratory distress, and pain. It is also speculated that SARS-CoV-2 affects the sensory nerves mediating cough, leading to hypersensitivity of the cough reflex. Assessing for pulmonary parenchymal fibrosis or bronchial damage due to mechanical ventilation is important as it may increase the hypersensitivity of the cough reflex, which can be evaluated using chest CT scans [34]. According to the guidelines of the Korean Academy of Asthma, Allergy, and Clinical Immunology, a detailed medical history, physical examination, and simple chest X-ray should be routinely conducted to assess chronic cough. Additionally, pulmonary function tests may be performed to differentiate chronic obstructive pulmonary disease. To exclude causes not identified on chest X-ray, chest CT and bronchoscopy can be performed. Additionally, fractional exhaled nitric oxide (FeNO) measurement is suggested for diagnosing cough-variant asthma and eosinophilic bronchitis [35]. However, the European Respiratory Society in 2019 advised against performing chest CT in the absence of specific findings on the chest X-ray, as the likelihood of bronchiectasis or pulmonary nodules, which are not identified on the chest X-ray, being the cause of cough is low. The measurement of FeNO was also deferred [36]. Recently, Kang et al. prospectively and retrospectively recruited patients who complained of persistent coughs following acute SARS-CoV-2 infection and compared them with a group of patients with chronic coughs unrelated to COVID-19. The authors found no differences in the severity of cough, simple chest X-rays, or pulmonary function tests and reported that in patients with persistent cough following COVID-19, there was a more frequent increase in FeNO, which may be associated with asthma or eosinophilic bronchitis [37]. Persistent cough following COVID-19 is a common symptom, yet specific evaluation methods and evidence are not clearly specified in various guidelines. Therefore, evaluation based on the clinical symptoms of chronic cough is recommended; notably, recommendations may change as new evidence emerges.

4) What are the evaluation methods for long COVID patients complaining of fatigue?

Recommendation
• Medical history-taking, physical examination, blood tests, electromyography, imaging tests of the musculoskeletal system, and 6MWT can exclude other organic causes that could explain fatigue. Applying fatigue scale assessment tools should be considered to evaluate the degree of fatigue symptoms (G, IIa).

Fatigue is the feeling of dullness, tiredness, or lack of energy [38]. The core of fatigue symptoms lies in the perception of having decreased ability of physical or mental functions due to impairment in the availability, utilization, or restoration of resources required to perform tasks [39]. After acute SARS-CoV-2 infection, the prevalence and prognosis of fatigue symptoms remain unknown. Fatigue is one of the common non-respiratory symptoms among patients with COVID-19. According to systematic literature reviews, the integrated prevalence of fatigue after COVID-19 varied from 45% to 64% [40-42]. In a large-scale study involving 1,142 hospitalized patients with COVID-19, 61% reported experiencing fatigue for up to 7 months after COVID-19 [43], and patients with higher severity requiring hospitalization or admission to the intensive care unit (ICU) continued to complain of persistent fatigue even after recovery from the acute phase [44-50]. However, this fatigue symptom following such viral infection cannot be simply explained as damage to organs. Risk factors for fatigue symptoms in patients with long COVID include being female and older age, although studies have reported inconsistent findings [51-57]. Anxiety, post-traumatic stress, and depressive symptoms are prevalent among survivors of respiratory virus infections, and particularly, depressive

Table 3. Chalder fatigue scale

1. Do you have problems with tiredness?
2. Do you need to rest more?
3. Do you feel sleepy or drowsy?
4. Do you have problems starting things?
5. Do you lack energy?
6. Do you have less strength in your muscles?
7. Do you feel weak?
8. Do you have difficulty concentrating?
9. Do you make slips of the tongue when speaking?
10. Do you find it more difficult to find the correct word?
11. How is your memory?

symptoms are associated with fatigue [58, 59]. The fatigue symptoms in patients with long COVID can be assessed through self-reporting or measured using fatigue assessment tools, and several criteria have been developed to explain the fatigue syndrome [38, 60, 61]. Fatigue symptoms can commonly be assessed using the Fatigue Severity Scale (FSS) and the Chalder Fatigue Scale (CFS) [62]. CFS is a self-report questionnaire designed to assess the severity and impact of fatigue in individuals, commonly used to measure fatigue in both clinical and research settings, and consists of 11 items that describe various symptoms associated with physical and mental fatigue (**Table 3**). Each item is scored on a Likert scale ranging from 0 to 3, where 0 represents "less than usual" and 3 represents "much worse than usual." The total score is calculated by summing the scores of each item, with higher total scores indicating higher levels of fatigue. Alternatively, the FSS can also be applied to evaluate the degree of fatigue in patients reporting fatigue symptoms (**Table 4**), and comprises 9 items, in which respondents rate their level of fatigue over the past week on a scale from 1 to 7 for each item. The final FSS score is determined by dividing the total sum by 9 to obtain the mean, with higher scores indicating greater fatigue levels.

When long COVID patients complain of fatigue during their visits, it is essential first to investigate psychological/emotional factors, medications, sleep disorders, and exposure to toxins that could contribute to the fatigue. Additionally, conducting a detailed medical history and physical examination to assess the presence of underlying conditions that may be associated with fatigue, sequelae from severe COVID-19, or other organic causes is also important [63]. Assessment of hospitalization treatment for patients who have had COVID-19, including evaluation of hospitalization duration and admission to the ICU, is necessary. Furthermore, a review of past medical history related to neurological, muscular, and skeletal disorders should be conducted, along with an assessment of the range of motion and stability of all major joints. As part of the neurological evaluation, assessments of muscle condition (*e.g.*, light touch, pinprick sensation, proprioception, and temperature sensation tests) are performed, along with gait evaluation (*e.g.*, tandem gait). For differential diagnosis, evaluations of muscle enzymes (such as creatine kinase, lactate dehydrogenase, and myoglobin), complete blood count, electrolyte panel, liver function tests, renal function tests, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests, serum cortisol, rheumatoid factor, and antinuclear antibodies are performed. In addition to blood tests, electromyography (EMG) can be performed, and, if necessary, CT scans or MRI can be performed to assess the presence of anatomical abnormalities in the musculoskeletal system. Functional assessments such as the 6MWT or sit-to-stand test can also be performed [3].

5) What are the evaluation methods for long COVID patients complaining of arthralgia and myalgia?

Recommendation

- If patients with long COVID complain of arthralgia and myalgia, blood tests, imaging studies, and other evaluations may be considered to differentiate underlying causes related to the symptoms (D, IIb).

Table 4. Fatigue severity scale

		Not at all						Very much so
1	When I am tired, I lose motivation.	1	2	3	4	5	6	7
2	Exercising makes me tired.	1	2	3	4	5	6	7
3	I get tired easily.	1	2	3	4	5	6	7
4	My physical activity decreases due to fatigue.	1	2	3	4	5	6	7
5	Fatigue often causes problems for me.	1	2	3	4	5	6	7
6	Continuous physical activity is difficult because of fatigue.	1	2	3	4	5	6	7
7	I cannot fulfill my work or responsibilities because of fatigue.	1	2	3	4	5	6	7
8	If I had to choose the three most challenging problems I face, fatigue would be one of them.	1	2	3	4	5	6	7
9	Fatigue interferes with my work, home life, and social activities.	1	2	3	4	5	6	7

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A domestic study conducted at 6 and 12 months post-COVID-19 diagnosis revealed that 11% of patients reported arthralgia after 6 months and 7% after 12 months, while myalgia was reported by 6% after 6 months and 2% after 12 months [12]. These findings are consistent with international studies, which identified arthralgia in 10 - 48% of patients from 4 weeks to 3 months post-infection, decreasing to 9% from 3 to 6 months, and myalgia in 1 - 32% from 4 weeks to 3 months, with a subsequent decrease to 11% from 3 to 6 months [64, 65]. Furthermore, a meta-analysis of patients who recovered from severe COVID-19 demonstrated that within the first year post-recovery, 5.7 - 18.2% experienced myalgia, and 4.6 - 12.1% experienced arthralgia [66]. In a study involving 189 individuals with persistent symptoms 6 weeks after COVID-19, serological tests for rheumatic conditions (such as anti-cardiolipin antibody, anti-nuclear antibody, and rheumatoid factor) showed no statistically significant differences compared to a control group [67]. However, due to the small sample size of patients reporting myalgia/arthralgia (11 and 6, respectively) in this study, definitive conclusions about the utility of serological tests for rheumatic diseases in patients with long COVID cannot be drawn. Additionally, an observational study of 20 patients with neuromuscular symptoms of long COVID revealed no abnormalities in nerve conduction studies, yet 55% (11/20) exhibited abnormalities in EMG [33]. However, given that the study results come from a small-scale observational study and that abnormalities were only detected in some cases, there is insufficient evidence to either recommend or restrict these tests for all patients with muscle pain symptoms in long COVID. Presently, no specific test is available to diagnose long COVID in patients with ongoing myalgia and arthralgia post-acute SARS-CoV-2 infection. The diagnosis of long COVID necessitates the exclusion of other potential diseases. Therefore, evaluations and testing for other diseases that may present similar symptoms should be conducted beforehand.

6) What are the evaluation methods for long COVID patients complaining of headaches?

Recommendation
• If a patient with long COVID complains of headaches, a neurological examination is recommended for evaluation (G, I). • If secondary headaches need to be differentiated, consideration should be given to neuroimaging studies of the brain, and it is recommended that the patient be referred to a neurologist for specialized evaluation and treatment (G, I).

Headache presents as a common symptom among COVID-19 patients, with reported prevalence ranging from 14% to 60%, persisting for weeks following the acute phase of the SARS-CoV-2 infection [68]. Meta-analytic studies indicate that 15% of patients continue to experience headaches three months after COVID-19 [69]. Headaches associated with long COVID may indicate either the worsening of pre-existing headaches or the emergence of new types. A notable feature is their persistence nature, often beginning around the time of COVID-19 diagnosis or shortly thereafter, occurring almost daily. The activation of immune/inflammatory responses during infection plays a role in headache manifestation, either by exacerbating pre-existing migraines or contributing to their chronicity [70]. Notably, headaches associated with long COVID tend to persist long after the acute viral infection, suggesting an indirect relationship with the SARS-CoV-2 virus itself [68]. Reports indicate similar occurrences of new persistent headaches lasting more than three months following viral infections such as the EBV and the Russian flu virus in 1890 [71, 72]. Further research is warranted to explore the similarities between newly developed persistent headaches following viral infections and those related to long COVID. When assessing headaches, it is crucial to exclude secondary headaches with organic causes. The initial assessment should begin with a thorough patient history to ascertain the nature of the headache, followed by a comprehensive neurological examination to identify any focal neurological abnormalities. Certain features such as fever, vomiting, or weight loss, accompanying headaches, those in cancer patients or those with immunosuppression, headaches with neurological abnormalities, or those accompanied by papilledema, or thunderclap headaches reaching peak severity within 1 min, new headaches after the age of 50, headaches that worsen over time, headaches occurring during the Valsalva maneuver or similar situations or headaches that worsen upon standing, warrant consideration of organic causes, thus requiring neuroimaging (MRI or CT) and referral to a neurologist for professional evaluation and treatment. When organic causes are ruled out, treatment follows the protocols for primary headaches [5, 73, 74].

7) What are the evaluation methods for long COVID patients complaining of cognitive impairment or brain fog?

Recommendation

- For cognitive impairment or brain fog (a condition characterized by difficulties with concentration and attention) in long COVID patients, it is recommended to conduct a detailed medical history, neurological examination, and neuropsychological assessment. Additionally, it is advised to discern potential underlying causes such as endocrine disorders, autoimmune diseases, infectious diseases, psychiatric conditions, sleep disorders, and medication side effects (G, I).
- Brain imaging tests are recommended if brain lesions are suspected or localized neurological abnormalities are detected (G, I).
- Clinicians should consider to consult a specialist with expertise in evaluating and correcting attention/concentration issues (G, IIa).

A meta-analysis investigating the prevalence of neurological symptoms occurring more than three months after the onset of COVID-19 revealed that brain fog was reported in 32% of patients (95% CI, 10.3 - 54.0), while memory decline was reported in 28% (95% CI, 21.5 - 35.4) [69]. Domestic studies investigating persistent symptoms 6 and 12 months after SARS-CoV-2 infection reported neurological symptom prevalence rates of 22% for concentration decline, 20% for memory decline, and 21% for cognitive decline [12, 75].

For cognitive symptoms related to long COVID, a detailed medical history, neurological examination, and neuropsychological testing should be considered, Brain imaging studies may be warranted if focal neurological abnormalities are present [5, 74]. Additionally, upon confirmation of cognitive decline, a comprehensive differential diagnosis should be pursued to explore potential underlying causes such as endocrine disorders, autoimmune diseases, infectious diseases, psychiatric conditions (including depression, anxiety, and post-traumatic stress disorder [PTSD]), sleep disorders, and medication side effects [3, 74]. **Table 5** presents representative medications that may affect cognitive function.

If neuropsychological testing reveals abnormalities or if focal neurological abnormalities require additional differential diagnosis, referral to neurologists or psychiatrists is recommended. Furthermore, for identified issues related to endocrine disorders, autoimmune diseases, infectious diseases, psychiatric conditions, or sleep disorders, further evaluation and treatment by the respective specialists are recommended [2, 3, 73-76].

Common symptoms reported by patients with brain fog (concentration/attention disorders) include difficulty concentrating on tasks, losing their train of thought, misplacing objects, making miscalculations, and being easily distracted. Neuropsychological assessment tools available include the digit span test, vigilance test, and letter cancellation test.

In cases of brain fog, assessment for conditions that may exacerbate symptoms is necessary, and additional testing and specialist referrals may be required. This includes areas such as sleep disorders, mood (including anxiety, depression, and post-traumatic stress disorder), fatigue, endocrine abnormalities, and autoimmune diseases. Referrals should be directed to the appropriate departments (such as psychiatry, neurology, rheumatology, endocrinology, etc.) based on the suspected condition. It is important to note that patients may express dissatisfaction with treatment if long COVID persists, possibly due to psychological factors. Mood disorders may manifest as secondary symptoms caused by long COVID or one of the various factors contributing to cognitive symptoms [74].

Table 5. Drugs that may affect cognitive function [74]

Category	Example drugs
Anticholinergics	
1st generation antihistamines	Diphenhydramine, hydroxyzine, meclizine
Antispasmodics	Scopolamine
Central nervous system agents	
Antidepressants	Amitryptyline, nortriptyline, paroxetine
Antipsychotics	Risperidone, quetiapine, olanzapine, ziprasidone
Benzodiazepines and sleep aids	Alprazolam, diazepam, lorazepam, temazepam eszopiclone, zaleplon, zolpidem
Muscle relaxants	Varisoprodol, cyclovenzaprine

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8) What are the evaluation methods for long COVID patients complaining of anxiety or depression?

Recommendation
• Immediate referral to psychiatry is recommended in cases of severe psychiatric symptoms, self-harm, or suicidal risk (G, I). • Referral to psychiatry is recommended for the exclusion of psychiatric conditions that may contribute to anxiety or depression (G, I).

International guidelines recommend urgent psychiatric evaluation for patients experiencing persistent COVID-19 symptoms or suspected post-COVID sequelae, particularly those exhibiting severe psychiatric symptoms or at risk of self-harm or suicide [2]. Additionally, assessments for anxiety, depression, and PTSD can assist in differentiating cognitive impairments from psychiatric conditions, with referrals to a mental health specialist being advisable. Various instruments such as the hospital anxiety and depression scale, Beck depression inventory, geriatric depression scale, and Korean version of the patient health questionnaire for depression (PHQ-2/9, or PHQ-8 omitting the item on suicidal thoughts if the immediate assessment is difficult), generalized anxiety disorder 7, and PTSD Checklist-5 are available for use [74].

A systematic literature review and meta-analysis examining the long-term neurocognitive effects of COVID-19 revealed that among the persistent symptoms, psychiatric symptoms such as PTSD (31%), depression (20%), and suicidality (2%) showed high prevalence rates [77]. A systematic literature review and meta-analysis comparing long-term effects between hospitalized and non-hospitalized COVID-19 survivors indicated that hospitalized individuals faced higher risks of long-term dyspnea (odds ratio [OR], 3.18; 95% CI, 1.90 - 5.32), anxiety (OR, 3.09; 95% CI, 1.47 - 6.47), myalgia (OR, 2.33; 95% CI, 1.02 - 5.33), and hair loss (OR, 2.76; 95% CI, 1.07 - 7.12) [78]. Additionally, a study administering the personality assessment inventory to measure psychological distress in 43 neuropsychological outpatients with long COVID found that somatic preoccupation and depression were the most significantly elevated symptoms [79].

Pre-existing neuropsychiatric or substance use disorders may exacerbate the progression of COVID-19 or heighten the risk of enduring complications [76, 80]. Patients admitted to isolation wards may experience reduced physical activity, a concern particularly problematic among the elderly [73]. A decrease in physical function can lead to an increase in mental health issues such as anxiety and depression. ICU admissions have been associated with long-term functional decline, PTSD, and increased rates of depression [81]. Anxiety disorders were reported in 17% of cases, while psychotic disorders occurred at a rate of 1.2%, with notably higher rates among patients who had been admitted to the ICU [82]. When treating patients with psychological or psychiatric symptoms, it is important to consider social factors such as poverty, discrimination, and social isolation [73]. Enhancing social connectedness, fostering social support networks, and implementing community-based measures can be beneficial for mental health and overall well-being.

9) What are the evaluation methods for long COVID patients complaining of sleep disorders?

Recommendation
• It is recommended to review sleep patterns and evaluate factors disrupting sleep conditions such as sleep apnea, restless leg syndrome, pain, and anxiety (G, I). • Clinicians should consider to consult a sleep medicine specialist for differential diagnosis of sleep disorders (G, IIa).

Meta-analyses of studies on COVID-19 patients have identified sleep disorders in 34% of cases, often coexisting with depression (45%) and anxiety disorders (57%) [83]. Further research suggests that disruptions in the sleep-wake cycle and circadian rhythms can adversely affect cognitive functions, including attention, concentration, learning, and memory, which are common concerns among patients with long COVID [84]. Systematic literature reviews and meta-analyses on the prevalence of sleep disorders among patients with long COVID have reported an overall prevalence of 46% (95% CI, 38 - 54%). Subgroup analysis indicated that poor sleep quality affected 56% of patients (95% CI, 47 - 65%), insomnia affected 38% (95% CI, 28 - 48%), and excessive daytime sleepiness was present in 14% (95% CI, 0 - 29%) of cases [85].

According to international guidelines, sleep disorder evaluations should include: 1) assessing sleep quantity and quality, challenges with sleep initiation, maintenance, or early waking, napping, daytime sleepiness, attention, concentration, memory, and decision-making, as well as the severity of symptoms (employing a sleep diary for a

minimum of two weeks to record specific sleep and wake patterns); 2) reviewing reports of sleep disturbances, including nightmares (indicative of PTSD), sleep apnea, restless legs syndrome, pain (muscle cramps and neuralgia), parasomnias, or daytime sleep episodes; 3) investigating additional factors that may disrupt sleep, such as exercise routines, physical activity limited by exertion, polypharmacy (use of four or more medications), high caffeine consumption, new supplement usage, increased alcohol intake, and anxiety; 4) evaluating current sleep habits through the use of sleep aids, hypnotics, blue light exposure, behavioral strategies, etc.; 5) additionally, considering sleep actigraphy as an objective assessment tool; 6) reviewing medications that can cause insomnia, including alcohol, antidepressants, beta-blockers, caffeine, chemotherapy drugs, cold and allergy medicines containing pseudoephedrine, diuretics, cocaine and other stimulants, nicotine, and stimulant laxatives; 7) assessing sleep patterns using tools such as the Epworth Sleepiness Scale, Stanford Sleepiness Scale, Patient-Reported Outcomes Measurement Information System, sleep scale surveys, and Insomnia Severity Index; 8) evaluating sleep apnea risk with the STOP-BANG questionnaire [63].

The likelihood of sleep disturbances may arise from acute stress following COVID-19, environmental factors during hospital stays, invasive medical interventions (such as mechanical ventilation), and the concurrent use of multiple medications [86]. A study conducted on 172 COVID-19 survivors who had been admitted to the ICU for treatment of acute respiratory distress syndrome investigated their sleep and circadian rest-activity patterns three months after discharge. Using the Pittsburgh Sleep Quality Index (PSQI) for evaluation, 60.5% exhibited poor sleep quality, as confirmed by sleep actigraphy. Female was associated with higher PSQI scores (P <0.05), and the use of invasive mechanical ventilation in the ICU was a significant predictor of increased fragmentation of the rest-activity rhythm (P <0.001). A decline in mental health measured by the Hospital Anxiety and Depression Scale was associated with poor sleep quality (P <0.001) [87].

Neuroimaging studies involving 35 COVID-19 patients who underwent PET-CT scans approximately 96 days post-diagnosis, compared with a control group, revealed metabolic reductions in specific brain regions. These reductions were associated with symptoms such as reduced sense of smell, anosmia, memory or cognitive impairment, pain, and insomnia [88].

10) What are the evaluation methods for long COVID patients complaining of dysphagia?

Recommendation
• If a patient with long COVID complains of dysphagia, diagnostic tests, such as a video-fluoroscopic swallowing study (VFSS) or fiberoptic endoscopic examination of swallowing (FEES), should be considered (G, IIa).

Approximately 30% of patients hospitalized with COVID-19 may require additional medical intervention due to dysphagia [89]. Risk factors include advanced age, chronic neurological or respiratory conditions, endotracheal intubation, mechanical ventilation, prolonged bed rest, persistent cognitive impairment, and pre-existing dysphagia. The occurrence of dysphagia post-COVID-19 may be associated with various factors, including tissue damage from medical device insertion, direct tissue damage from SARS-CoV-2 infection, secondary neuropathy, as well as muscle weakness related to swallowing [90]. Early diagnosis is crucial as dysphagia can increase the risk of aspiration pneumonia. Preliminary screening tests can be helpful before conducting confirmatory tests. According to clinical guidelines established by the Korean Academy of Rehabilitation Medicine and the Korean Dysphagia Society, the 3-ounce water swallowing test can be used for screening. If a high risk of aspiration is identified during the test, standard screening tests such as the Burke Dysphagia Screening Test, Gugging Swallowing Screen, Standardized Swallowing Assessment, Toronto Bedside Swallowing Screening Test, and Clinical Functional Scale for Dysphagia can be performed [91]. Confirmatory tests include the VFSS and the FEES, which can be conducted complementarily based on the patient's condition.

11) What are the evaluation methods for long COVID patients complaining of olfactory or gustatory disorders?

Recommendation
• If a patient with long COVID complains of smell and taste disturbances, it is recommended to rule out other organic causes (G, I).

In cases of persistent olfactory and gustatory disorders following a COVID-19 diagnosis, organic causes must first be ruled out. When gustatory disorders are reported, assessing the possibility of oral or dental diseases

causing the impairment should be prioritized. Since most gustatory symptoms are linked to olfactory disorders, verification of any olfactory disorder is also necessary. If a patient complains of olfactory impairment, evaluating the likelihood of allergic rhinitis or chronic rhinosinusitis should be given priority. Additionally, assessment for head trauma or neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, or mild cognitive impairment, is necessary. It is crucial to ascertain whether the patient is taking medications that could induce olfactory disorders, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or dihydropyridine calcium channel blockers [92].

Current research on the assessment of olfactory and gustatory disorders in COVID-19 patients remains insufficient. In a systematic literature review conducted by Annelin et al. focusing on qualitative olfactory function assessment, 72 studies were analyzed [93]. Of these, only four objective assessment tools were used for olfactory function: the Chemosensory Perception Test, Yale Jiffy Smell Identification Test, SCENTinel 1.1, and the Sniffin' Sticks Test. Conversely, subjective assessment tools such as the National Health and Nutrition Examination Survey, Questionnaire of Olfactory Disorders, and the Global Consortium for Chemosensory Research questionnaire were more commonly employed [93]. While objective assessments have the advantage of providing consistent data, they are limited in their inability to evaluate phantosmia, the sensation of non-existent odors. Currently, there is insufficient evidence to determine the superiority of any assessment tool.

The pathogenesis of olfactory and gustatory disorders is attributed to the SARS-CoV-2 infection of olfactory epithelial cells expressing angiotensin-converting enzyme-2 (ACE2), leading to damage to olfactory nerve cells. While olfactory and gustatory disorders generally recover over weeks to months, a parametric treatment model study conducted through a systematic literature review by Benjamin et al. revealed that approximately 5% of patients experienced persistent functional impairment [94]. Notably, women had a lower likelihood of recovering smell and taste. Long-term follow-up studies are necessary to comprehensively understand the trajectory of olfactory and gustatory disorders.

12) What are the evaluation methods for long COVID patients complaining of PESE?

Recommendation
• If a patient with long COVID complains of PEM or PESE, a questionnaire should be used to assess whether they have a movement disorder, and cardiopulmonary exercise testing may be considered as a confirmatory test (G, IIb).

'PEM' also known as 'PESE', describes the exacerbation of symptoms or the emergence of new symptoms following physical or cognitive activity. PEM/PESE represents a distinctive set of symptoms that differs from the fatigue experienced by healthy individuals after overexertion. Symptoms may worsen during exercise and can manifest at various times, ranging from hours to months after SARS-CoV-2 infection. PEM/PESE may occur in response to activities previously manageable (*e.g.*, showering, cooking, conversing, or reading), and can be induced in previously healthy individuals [95]. The precise pathophysiology of PEM/PESE remains incompletely understood but is known to result from various bioenergetic dysfunctions (*e.g.*, abnormal endothelial responses; changes in brain function and cognitive impairment; orthostatic intolerance; alterations in methylation and acetylation affecting gene expression and protein function; changes in the gut microbiome) [96].

A 10-item questionnaire can be used for screening PEM/PESE (**Fig. 1**). Suspected cases based on the questionnaire responses can undergo a comprehensive evaluation using the DePaul Post-Exertional Malaise Questionnaire (DQS-PEM) [97]. The DQS-PEM consists of 53 questions (items 13 - 66) and uses a Likert scale from 0 to 4 to assess the frequency and intensity of symptoms, allowing for the identification of triggers, symptoms, accompanying outcomes, and duration of manifestation. When patients present fatigue suspicious of PEM/PESE, a series of tests can be used to assess their exercise and strength levels. Anaerobic exercise capacity can be evaluated with the '30-second sit-to-stand test,' aerobic exercise capacity with 'CPET,' and muscle strength with the 'handgrip test'. The application of 'graded exercise therapy' under clinical supervision, which involves gradually increasing physical activity, may lead to functional decline in PEM/PESE patients [98]. Therefore, conducting two consecutive days of CPET can reveal a different response in PEM/PESE patients compared with healthy individuals. Specifically, PEM/PESE patients show an inability to increase myocardial

Symptoms	Frequency: Throughout the past 6 months, how often have you had this symptom? For each symptom listed below, circle a number from: 0 = none of the time 1 = a little of the time 2 = about half the time 3 = most of the time 4 = all of the time					Severity: Throughout the past 6 months, how much has this symptom bothered you? For each symptom listed below, circle a number from: 0 = symptom not present 1 = mild 2 = moderate 3 = severe 4 = very severe				
1. Dead, heavy feeling after starting to exercise	0	1	2	3	4	0	1	2	3	4
2. Next day soreness or fatigue after non-strenuous, everyday activities	0	1	2	3	4	0	1	2	3	4
3. Mentally tired after the slightest effort	0	1	2	3	4	0	1	2	3	4
4. Minimum exercise makes you physically tired	0	1	2	3	4	0	1	2	3	4
5. Physically drained or sick after mild activity	0	1	2	3	4	0	1	2	3	4
6. If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?	Yes					No				
7. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal physical effort?	Yes					No				
8. Do you experience a worsening of your fatigue/energy related illness after engaging in mental effort?	Yes					No				
9. If you feel worse after activities, how long does this last?	≤1 h		2 - 3 h		4 - 10 h	11 - 13 h		14 - 23 h		≥24 h
10. If you do not exercise, is it because exercise makes your symptoms worse?	Yes					No				

Figure 1. Screening questionnaire for post-exercise malaise or post-exertional symptom exacerbation [99].

workload, oxygen consumption, heart rate, and systolic blood pressure during the second test compared to the first.

13) What are the evaluation methods for long COVID patients complaining of postural tachycardia syndrome (POTS)?

Recommendation

- If a patient with long COVID complains of postural tachycardia symptoms, an active standing test (NASA Lean Test) or head-up tilt test may be considered (G, IIb).

'POTS' refers to chronic symptoms lasting more than 6 months, triggered upon standing. It is characterized by an increase in heart rate of over 30 beats per minute or a heart rate exceeding 120 beats per minute from a supine to standing position without hypotension [100]. Autonomic dysfunction post-COVID-19 may be related to various causes such as immune dysregulation, hormonal disturbances, viral penetration into the central nervous system, elevated cytokines, direct tissue damage, endotheliitis, micro-thrombosis, and persistent infection [101]. Predominant symptoms observed in POTS include

palpitations and chest pain. Exercise intolerance, fatigue, and vasovagal syncope have also been reported. If POTS symptoms are suspected, the NASA Lean Test or head-up tilt test is used to monitor changes in heart rate and blood pressure from supine to standing positions [102]. During these tests, about 50% of patients exhibit acrocyanosis (purple discoloration of the extremities). If POTS diagnosis remains uncertain, further assessments such as the Valsalva maneuver test and deep breathing test can be conducted. Furthermore, inflammatory or autoimmune markers like G-protein-coupled receptor (alpha adrenoreceptor, beta-adrenoreceptor, angiotensin II, nociceptin, and muscarinic) antibodies, ganglionic neuronal nicotinic acetylcholine receptor antibody, circulating anti-nuclear antibody, antithyroid antibody, anti-NMDA-type glutamate receptor antibody, anti-opioid like-1 receptor antibody, anti-cardiac protein antibody, anti-phospholipid antibody, and Sjögren's antibody may be measured [103]. Standard laboratory tests including complete blood count, albumin, renal function, electrolytes, NT-proBNP, thyroid-stimulating hormone, and morning cortisol levels are recommended. A 24-hour Holter monitoring test can also aid in the diagnosis of POTS. To rule out other conditions, 24-hour ambulatory blood pressure monitoring, chest X-ray, echocardiography, chest CT, cardiac MRI, and treadmill test should be considered [104]. In cases with severe disability, a 6MWT can be performed to assess peripheral oxygen desaturation and flat breathing responses.

5. TREATMENT

(1) What are the treatment approaches for different symptoms of long COVID?

1) How is dyspnea treated in long COVID patients?

Recommendation
• To manage dyspnea reported by patients with long COVID, adjustments in the dosage or frequency of previously used medications (*e.g.*, inhalers) may be considered, or specific treatment for newly diagnosed conditions can be initiated (C, IIb).

Although guidelines published in other countries have not specifically recommended a dedicated treatment for dyspnea in patients with long COVID, some studies suggest that respiratory rehabilitation can be beneficial in the absence of other dyspnea-inducing conditions [105-112]. The cause of persistent dyspnea should be evaluated, and if a new condition is diagnosed, appropriate treatment should be applied. A retrospective observational study conducted in Spain monitored 76 hospitalized COVID-19 patients and conducted a follow-up telephone survey regarding their symptoms one year later [113]. The study revealed that although the majority of symptoms improved more in the group treated with steroids during the acute phase of SARS-CoV-2 infection, dyspnea and cough remained similar between those who received steroids and those who did not. In a prospective, randomized observational study in Türkiye, 30 patients with persistent dyspnea and cough for more than three months, along with confirmed pulmonary fibrosis after COVID-19 were treated with either nintedanib or pirfenidone over three months [114]. Their pulmonary functions, 6MWT, and oxygen saturation were compared. Both groups showed improvements in imaging findings and pulmonary function. However, the nintedanib group showed greater improvements in exercise capacity and oxygen saturation, but with more adverse drug reactions. Another prospective observational study in the UK evaluated 49 patients with mild acute COVID-19 followed by long COVID, 26 of whom received antihistamine treatment (H1 receptor blockade: loratadine 10mg or fexofenadine, H2 receptor blockade: famotidine or nizatidine) [115]. The study found that 72% of treated patients showed significantly better symptom improvement compared to 26% (n = 23) who did not receive antihistamines, between 4 to 16 weeks after treatment initiation. Blood tests in patients with long COVID showed reduced CD4+ and CD8+ T-cell counts; however, this did not predict the response to antihistamine treatment.

2) How is cough treated in long COVID patients?

Recommendation
• For the cough symptoms in patients with long COVID, empirically, antihistamines and intranasal corticosteroid use may be considered (G, IIb).

No specific drugs have been recommended for the treatment of cough in patients with long COVID. A recent Korean study compared the clinical characteristics of 120 patients with persistent cough (≥3 weeks) since contracting COVID-19 and 100 patients with chronic cough unrelated to COVID-19 during the Omicron outbreak [37]. The two groups generally had similar clinical characteristics; however, a significant increase in FeNO was observed in patients with chronic cough post-COVID-19 infection. On the other hand, a paradigm shift exists in understanding

chronic cough, where it is viewed not as a symptom of other diseases but as an independent condition stemming from hypersensitivity of the cough reflex circuit, and in reflection of such a view, the Korean Academy of Asthma, Allergy and Clinical Immunology developed chronic cough treatment guidelines in 2018 [35]. These guidelines recommend H1 antihistamines as the primary empirical treatment for the treatment of nonspecific chronic cough without treatable traits. Short-term (2 - 4 weeks), high-dose inhaled corticosteroids can be considered. However, objective testing for asthma and eosinophilic bronchitis is recommended before treatment. The empirical use of leukotriene receptor antagonists and proton-pump inhibitors is not recommended due to insufficient evidence [35]. Most guidelines are based on a limited number of studies, and considering the significant placebo effect and natural improvement in cough, clinical trials are challenging. Thus, cough in patients with long COVID should adhere to the existing treatment guidelines, and further research is necessary.

3) How is fatigue treated in long COVID patients?

Recommendation
• For fatigue symptoms in patients with long COVID, correctional therapy of the underlying causes is necessary. If no specific underlying causes exist, rehabilitation therapy may be considered (G, IIb).

Various modalities, including drugs, alternative medicine, cognitive behavioral therapy, and exercise have been considered for the treatment of fatigue symptoms in patients with long COVID. However, due to reasons such as the heterogeneity in study designs, durations, methods of fatigue assessment, and treatment outcomes, high-level evidence to support the effectiveness of these treatments and interventions is lacking [3]. If neurological abnormalities (*e.g.*, myopathy, gait instability) are identified in patients complaining of fatigue, a referral to a neurologist is recommended. In cases where musculoskeletal abnormalities or inflammatory myopathies are detected, an orthopedic surgeon or rheumatologist should be consulted. For patients where no other organic cause of fatigue is identified, rehabilitation treatments such as muscle strengthening, stretching, balance training, gait training, aquatic therapy, yoga, and physical therapy can be considered [63]. Additionally, occupational therapy may be performed. For patients requiring assistive equipment for rehabilitation or fatigue, suitable devices or adaptive aids could be recommended [116]. If symptoms persist without an organic cause, a psychiatrist or clinical psychologist can be consulted [2]. Some studies have suggested potential benefits of taking rintatolimod, as well as counseling and graded exercise therapy; however, the evidence is limited [117, 118]. Telemedicine follow-ups could be beneficial for patients with long COVID who complain of fatigue [62].

4) How is arthralgia or myalgia treated in long COVID patients?

Recommendation
• For treating joint and muscle pain in patients with long COVID, referral to a related specialist may be considered (D, IIb).

To date, well-established meta-analyses RCT are lacking on the treatment of myalgia or arthralgia in patients with long COVID. A set of guidelines published in another country suggest that low-dose naltrexone may be considered for neuropathic pain, chronic joint pain, fatigue, and other pain caused by autonomic anomaly in patients with long COVID [119]. However, those guidelines used a study conducted on patients with chronic complex regional pain syndrome, and not patients with long COVID, as evidence. Thus, evidence supporting the use of low-dose naltrexone in patients with long COVID is insufficient [120]. Referral to relevant specialists may be considered for persistent pain in order to rule out causes other than long COVID and to treat the condition.

5) How is headache treated in long COVID patients?

Recommendation
• After excluding secondary headaches, symptomatic treatment is provided for primary headaches. In particular, if migraine-like symptoms persist and interfere with daily life, preventive treatment for migraines should be considered (G, IIa).

Little evidence is available on the appropriate treatment methods for headaches related to long COVID. For primary headaches that existed prior to COVID-19 and were exacerbated by the infection, symptomatic and preventive treatment could be considered based on the patient's individual characteristics and their headache [121]. For new daily persistent headaches or headaches meeting the diagnostic criteria for chronic headaches due to systemic infection, migraine prevention treatments can be considered if the clinical phenotype resembles that of

migraines. The risk of medication overuse headache is high in long COVID-related headaches due to their daily persistence. Medication overuse headache may occur if triptans or opioid analgesics are used more than 10 days per month, or simple analgesics more than 15 days per month, over three months. Therefore, educating patients about this risk and considering appropriate preventive treatments is crucial [121]. During a headache attack, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans can be used as treatment for acute episodes. Despite initial concerns about the safety of NSAIDs in COVID-19 patients due to their potential role in overexpressing ACE2, they are safe for use for mild headache attacks [122]. For moderate to severe headache episodes, triptans can be considered. **Table 6** presents a list of most commonly used drugs to treat headaches. If the headache is related to mood disorders, sleep disturbances, or stress due to socioeconomic difficulties, flunarizine and beta-blockers could worsen depression symptoms. Topiramate should be used with caution in patients with long COVID experiencing cognitive decline or memory loss, as it may lead to cognitive impairment [74, 122]. In addition to pharmacological treatment, lifestyle modifications, such as maintaining a regular lifestyle, exercising, and avoiding long periods of fasting, are essential [121]. Especially, addressing sleep problems that are common post-COVID-19 may be helpful in controlling headaches, as sleep problems are associated with headaches [5, 75, 123].

6) How are cognitive impairments or brain fog (reduced concentration and attention) treated in long COVID patients?

Recommendation

- Patients who are found to have objective symptoms of cognitive impairment during cognitive screening are recommended to be referred to a specialist for further evaluation and treatment (G, I).
- If there are suspected causes that may induce cognitive impairment or brain fog (decreased concentration/attention) symptoms, such as medication side effects, neurological disorders, endocrine disorders, autoimmune or infectious diseases, mood disorders, or sleep disorders, clinicians should consider to consult relevant specialists (G, IIa).

Specific evidence for pharmacological treatments and management of cognitive impairment in patients with long COVID is still lacking [5, 74]. Treating conditions that potentially contribute to cognitive impairment, such as sleep disorder, pain, and mood disorder (*e.g.*, depression, anxiety) should be considered [73-76]. Furthermore, regular exercise may be effective in improving sleep disorders and cognitive function [74]. Monitoring the symptoms after patients returning to their daily activities (*e.g.*, school, work) is important. For those who are found to have objective cognitive impairment on cognitive screening tests, referral to a specialist should be considered for further cognitive evaluation and treatment [73, 74, 76].

Therapeutic interventions for reduced attention/concentration include attention process training for verbal and nonverbal tasks, metacognitive strategies, timed-structured activities, and techniques to minimize distractions [74].

Table 6. Commonly used drugs for headaches [124]

	Drug	Mechanism	Daily dose range	Adverse effects
Preventive drugs	Propranolol	Beta blocker	20 - 160 mg	Fatigue, dizziness, depression, vivid dreams
	Flunarizine	Calcium channel blocker	5 - 10 mg	Weight gain, drowsiness, dry mouth, dizziness, hypotension, depression, Parkinson's disease
	Amitriptyline	Tricyclic antidepressant	2.5 - 50 mg	Weight gain, constipation, dizziness, asthenia, dizziness, drowsiness, fatigue, visual disturbance, dry mouth
	Topiramate	Anti-epileptic	12.5 - 150 mg	Paresthesia, weight loss, memory impairment
Acute-phase drugs	Frovatriptan	Triptan	2.5 - 5 mg	Triptan sensation (various unpleasant sensations caused by triptan, including tingling, throbbing, strange feelings, sensations of heat or burning, coldness, pressure or tightness in body parts, including the neck and chest), dizziness, drowsiness, fatigue, asthenia, nausea
	Naratriptan	Triptan	1 - 2 mg	Triptan sensation, dizziness, drowsiness, fatigue, asthenia, headache, nausea
	Zolmitriptan	Triptan	2.5 - 7.5 mg	Triptan sensation, dizziness, drowsiness, fatigue, asthenia, headache, nausea

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7) How are anxiety or depressive symptoms treated in long COVID patients?

Recommendation
• If there are severe psychiatric symptoms or a risk of self-harm or suicide, immediate psychiatric consultation is recommended (G, I). • Referral to a psychiatrist is recommended for the purpose of ruling out psychiatric conditions that may explain anxiety or depression (G, I). • When a patient with long COVID exhibits depressive symptoms, the prescription of selective serotonin reuptake inhibitors (SSRIs) may be considered (C, IIb).

Fluvoxamine is a SSRI that has been primarily used to treat depression, anxiety disorders, and compulsive disorders. In recent years, however, it has been proposed to be a promising anti-COVID drug due to its anti-inflammatory effects. A study that evaluated the effects of fluvoxamine on the neuropsychiatric symptoms in long COVID showed that the administration of fluvoxamine in the acute phase of SARS-CoV-2 infection reduces fatigue, while it did not have significant effects on other symptoms [125]. In Italy, the use of SSRIs in 92% of 60 patients complaining of major depression episodes following COVID-19 infection led to a reduction by more than 50% in the Hamilton Depression Rating Scale score four weeks later [126]. Clomipramine, tricyclic antidepressants that have anti-inflammatory effects and penetrate the central nervous system, have been proposed as potential therapeutics for the central nervous system symptoms in COVID-19; however, its efficacy has not been documented in RCTs [127].

8) How are sleep disorders treated in long COVID patients?

Recommendation
• If there is a sleep disorder, it is recommended to eliminate factors that disturb sleep (habits, use of substances, the environment, etc.) and identify and address causative conditions (such as sleep apnea, restless legs syndrome, pain, anxiety, etc.) (G, I). • Clinicians should consider to refer to a sleep medicine specialist (G, IIa). • Clinicians should consider to treat patients with cognitive-behavioral therapy, pharmacotherapy, and sleep diaries (G, IIa).

According to international guidelines, the management of insomnia requires a stepwise approach aiming to eliminate or minimize contributing factors and comorbid conditions (*e.g.*, obstructive sleep apnea). Behavioral and pharmacological treatments for insomnia can be successful when all contributing factors are identified and addressed. Most patients with insomnia related to long COVID enter the chronic phase of insomnia. The preferred initial treatment in this phase is cognitive behavioral therapy for insomnia (CBT-I), which is a multifaceted approach targeting thoughts and behaviors related to sleep problems. Behaviorally, patients are encouraged to establish stable bed and wake times, lie in bed only when sleeping, foster a comfortable sleeping environment, avoid substances that disrupt sleep, reduce time in bed, and get out of bed when experiencing heightened states of anxiety. CBT-I addresses insomnia and anxious and catastrophic thoughts related to sleep expectations, and promotes relaxation such as progressive muscle relaxation, mindfulness, and meditation. Although CBT-I has been validated as an in-person therapy, online or telemedical regimens have demonstrated promising results in a small study [63]. A systematic review using the Pittsburgh Sleep Quality Index (PSQI) as an outcome variable to understand the effects of non-pharmacological interventions (NPIs) on improving sleep quality in healthy or chronically ill populations found that NPIs, such as resistance exercise (standardized mean differences [SMD], -0.29; 95% CI, -0.64 to 0.05; P = 0.09), yoga (SMD, -0.48; 95% CI, -0.72 to -0.25; P <0.0001), cognitive behavioral therapy (SMD, -1.69; 95% CI, -2.70 to -0.68; P = 0.001), music (SMD, -1.42; 95% CI, -1.99 to -0.85; P <0.00001), and blue light (SMD, -0.43; 95% CI, -0.77 to -0.09; P = 0.01) improved overall PSQI scores [128].

9) How is dysphagia treated in long COVID patients?

Recommendation
• As for the dysphagia associated with long COVID, clinicians should consider swallowing rehabilitation exercises, neuromuscular electrical stimulation therapy, and improving the nutritional status for the patients (G, IIa).

Existing guidelines do not specify treatment modalities for dysphagia in the context of long COVID, and they mention the use of general dysphagia treatment modalities. The guidelines developed by the Korean Academy of Rehabilitation Medicine and the Korean Dysphagia Society highly recommend tongue and pharyngeal muscle strengthening exercises, neuromuscular electrical stimulation, and nutritional interventions to improve

swallowing function [91]. Additionally, expiratory muscle strength training, compensatory swallowing technique training, transient receptor potential channel stimulation with drugs, biofeedback training, and specific treatment for cricopharyngeal dysfunction are mentioned as potential interventions. Referral to a dysphagia specialist is advised for detailed treatment regimens.

10) How are olfactory and gustatory disorders treated in long COVID patients?

Recommendation
• For patients with long COVID, olfactory training is recommended to improve olfactory dysfunction (A, I). • For patients with long COVID, topical corticosteroid nasal sprays may be considered to improve olfactory dysfunction (A, IIb).

Gustatory disorders due to COVID-19 generally improve over time; currently, research evidence to support specific treatments for gustatory disorders is lacking. Since olfactory nerves can regenerate, repeated olfactory training can aid in recovery. A systematic review of RCTs assessing the effectiveness of various treatments for olfactory disorders revealed that olfactory training was strongly recommended, along with smoking cessation in 11 out of 15 studies [129]. Another meta-analysis also confirmed the effectiveness of olfactory training in improving olfactory function [130]. Traditional olfactory training involves sniffing four distinct scents—rose, eucalyptus, clove, and lemon—for 20 - 30 seconds each and recording the experience. This training is cost-effective and can be performed at home, with no systemic side effects, making it a viable option for treating olfactory disorders. If no improvement is observed despite olfactory training, referral to a specialist is advised.

Several studies have evaluated the effectiveness of steroid therapy for olfactory disorders in COVID-19 patients [130-132]. A RCT showed that systemic steroids (starting with prednisolone at 1mg/kg/day and tapering over 15 days) and local betamethasone nasal irrigation treatment significantly improved olfactory function compared to a control group [131]. Furthermore, a RCT by Masoumeh et al. showed a significant increase in olfactory scores with local corticosteroid nasal spray treatment [132]. However, a meta-analysis found no significant difference in olfactory recovery between those who exclusively underwent olfactory training and those who combined it with corticosteroid nasal spray treatment [130]. Local steroid therapy can be cautiously considered to improve olfactory disorders in patients without contraindications to steroids.

11) How are PEM or PESE treated in long COVID patients?

Recommendation
• In cases where there is discomfort after exercise in patients with long COVID, educating on the importance of alternating between appropriate activity and rest may be helpful (G, IIb).

Patients without PEM or PESE can proceed with physical strength-building therapies to recover their physical functions [133]. However, in patients with PEM or PESE, gradually increasing exercise or activity levels can cause physical and emotional harm, and may sometimes show irreversible outcomes, potentially accelerating the progression of the disease [134]. Clinicians should not force patients experiencing PEM/PESE to increase their activity levels and should instead encourage them to stop working and rest.

Currently, no precise treatment has been established for symptoms of PEM/PESE following SARS-CoV-2 infection. Data suggests that "pacing" can lead to less severe symptoms, improved quality of life, better physical function, and less fatigue [134]. Pacing involves accurately assessing physical, mental, and emotional resources while making space for uncontrollable factors, and repetitively adjusting rest and activity as needed. The components constituting a sustainable activity level vary among individuals, and personal thresholds can gradually change. Preventing and alleviating PEM/PESE includes planning rest before and after intense activities and building awareness of daily activity levels that do not trigger the recurrence of PEM/PESE symptoms [135].

12) How is POTS treated in long COVID patients?

Recommendation
• When patients with long COVID complain of POTS symptoms, non-pharmacological and pharmacological treatments may be considered depending on their hemodynamic status (G, IIb).

Upon diagnosis of POTS, non-pharmacological treatment is first considered (**Table 7**). However, adequate symptom control is challenging in most cases, in which case pharmacological treatment is considered depending

Table 7. Treatment for POTS [138]

Non-pharmacologic treatment
• Water intake: 2 - 3 L/day. • Oral NaCl intake: 10 - 12 g/day. • 20 - 40 mmHg compression braces. • Focus on the abdomen and legs. • Sleep with the head raised (10°). • Drink water before getting out of bed in the morning. • Exercise training: simple isometric, aerobic, and resistance exercises. • Avoid situations that may exacerbate symptoms: sleep deprivation, exposure to a hot or cold environment, alcohol consumption, overeating, prolonged meals, standing up, anemia, and dehydration. • Educate patients that POTS is a dynamic condition and that there is a risk for infection. • Move slowly when standing up from a lying or sitting position. • Skeletal muscular pump to increase venous flow and prevent syncope. • Eat frequent small meals and reduce consumption of refined carbohydrates. • Maintain blood glucose balance and prevent postprandial hypotension.
Pharmacological treatment
• Fludrocortisone 0.1 - 0.2 mg/day • Desmopressin 0.1 - 0.2 mg • Erythropoietin 10,000 IU/week • Propranolol 10 - 20mg up to 4 pills/day • Ivabradine 2.5 - 7.5/12 hours • Pyridostigmine 30 - 60 mg up to 3 pills/day • Midodrine 2.5 - 15 mg 3 times/day • Octreotide 10 - 30 mg intramuscular injection • Droxidopa 100 - 600 mg/8 hours • Methyldopa 125 - 250 mg/12 hours • Clonidine 0.1 - 0.2 mg oral patch • Normal saline, verapamil, omega-3 fatty acid supplementation • Intravenous immunoglobulin and plasmapheresis
Noninvasive neuromodulation

on the patient's hemodynamic status [136]. For the tachycardia phenotype, beta-blockers such as ivabradine and metoprolol may be considered, and for the hypotensive phenotype, midodrine, pyridostigmine, and droxidopa may be considered. For the hyperadrenergic phenotype, clonidine or methyldopa may be considered. For persistent symptoms even with non-pharmacological and pharmacological treatment, noninvasive neuromodulation emerged as an favorable option in recent years. Modalities such as cognitive behavioral therapy, breathing retraining, and paced postural exercise have been proposed [137].

(2) Should prophylactic anticoagulants be used in long COVID patients?

Recommendation
• The use of anticoagulants or antiplatelet drugs for the purpose of preventing blood clots is not recommended (C, III). • However, if a blood clot is diagnosed, treatment with anticoagulants or antiplatelet drugs is recommended according to the relevant guidelines (A, I).

For adult patients with COVID-19 who require hospitalization (excluding pregnant women), low molecular heparin or unfractionated heparin is recommended [24]. However, these recommendations are limited to the treatment in the acute phase of COVID-19, and the evidence to expand these recommendations to patients with long COVID is limited. The 30-day incidence of thrombosis in patients with long COVID is low, standing at 2.5%, and similar to the incidence of hemorrhagic complications [62]. A multicenter RCT conducted in Brazil on patients with COVID-19 at a risk of thrombosis reported that the group receiving rivaroxaban (10 mg/day) until 35 days post-discharge had a significantly lower incidence of thrombosis compared to the control group [139]. However, a large-scale prospective, multicenter, randomized double-blind placebo trial conducted in the United States reported that the 30-day incidence of thrombosis was low and not significantly different between the group that received apixaban (2.5 mg) twice daily for 30 days (2.13%) and the placebo group (2.30%) [140]. These studies considered extending thromboprophylaxis up to 45 days, with no evaluation of long-term administration [3]. Consequently, the evidence to routinely recommend long-term anticoagulation or antiplatelet therapy for thromboprophylaxis in patients with long COVID is insufficient. Decisions regarding thrombosis prevention in these patients should be based on a careful consideration of underlying conditions and the general risks of thrombosis versus bleeding. If anticoagulation is deemed necessary for thromboprophylaxis, evidence supporting the use of a dose beyond the standard treatment dosing is lacking; this may increase the risk of bleeding. Thus, the use of therapeutic doses of anticoagulants is not recommended [24]. If dyspnea persists without significant abnormalities in the lung parenchyma, it is necessary to follow guidelines and assess for pulmonary embolism [62]. If thrombosis is confirmed, the decision to administer anticoagulants or antiplatelet agents should be made in accordance with relevant guidelines [141].

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(3) Is the administration of systemic steroids helpful for long COVID patients?

Recommendation
• If there are no other conditions necessitating steroid use in patients with long COVID, the administration of systemic steroid is not recommended (D, III).

A study revealed that the individuals who received steroids during the acute phase of SARS-CoV-2 infection experienced lower incidences of widespread pain and psychiatric abnormalities one year later compared to those who did not use steroids [113]. However, it was an observational study, involving a small sample size of 76 patients, and it did not specify the indications for steroid use during the acute phase of SARS-CoV-2 infection. Furthermore, patients who died or had cognitive impairments were excluded, indicating potential selection bias, which greatly reduces the reliability of the study results. Therefore, the evidence supporting the use of steroids to prevent long COVID in patients with acute SARS-CoV-2 infection is inadequate. Moreover, the NIH COVID-19 treatment guidelines strongly recommend against the use of systemic steroids in patients with acute SARS-CoV-2 infection unless a clear indication exists, except the need for oxygen, excluding the prevention of long COVID [142]. The effectiveness of systemic steroids in preventing long COVID during the acute phase of SARS-CoV-2 infection remains unclear, and their use is not recommended due to potential adverse effects.

(4) Is the administration of anti-fibrotic drugs necessary in long COVID patients?

Recommendation
• If pulmonary fibrosis is suspected in patients with long COVID, chest CT is recommended to assess the degree of pulmonary fibrosis (A, I). • The use of antifibrotic drugs is not recommended without confirming the degree of pulmonary fibrosis (G, III).

Existing guidelines do not address the treatment of pulmonary fibrosis in patients with long COVID complications. Diagnosis of pulmonary fibrosis, a sequela of chronic COVID-19, should precede treatment and can be achieved through diagnostic methods such as chest CT scans. Although some reports propose initiating treatment upon confirmation of the extent of pulmonary fibrosis, insufficient evidence exists regarding the optimal drugs and treatment duration for this condition. Most results have shown that nintedanib yields superior outcomes compared to perfenidone. However, further research is warranted due to potential differences in the results depending on the underlying pulmonary disease. Additionally, the use of anti-fibrotic drugs necessitates consideration of pre-existing pulmonary conditions, with reports suggesting active treatment with anti-fibrotic drugs in the presence of pre-existing pulmonary fibrosis [114, 143-145].

(5) Is respiratory rehabilitation therapy necessary for long COVID patients?

Recommendation
• Respiratory rehabilitation therapy is recommended for patients with long COVID, considering underlying lung conditions, the need for ICU treatment, the presence of comorbidities (neurological and muscular disorders), and other relevant factors (A, I).

Although the number of patients is limited, several countries have conducted RCT on respiratory rehabilitation therapy for patients with long COVID. These studies have employed various rehabilitation treatments, resulting in inconsistent outcomes. For instance, a RCT conducted in the United States examined the effect of electrical stimulation (E-slim) on 18 individuals diagnosed with lower extremity muscle weakness related to PASC after COVID-19 hospitalization. The study, which divided participants into an E-slim application group and a control group, observed improvements in plantar oxyhemoglobin and gastrocnemius muscle endurance in the E-slim group compared to the control group after four weeks of treatment [105]. Similarly, an RCT in Poland compared traditional respiratory rehabilitation conducted in a hospital setting to virtual reality-based respiratory rehabilitation over three weeks, five times per week at high intensity [106]. This trial evaluated pulmonary function, symptoms of dyspnea, exercise capacity (via the 6MWT and walking distance), and perceived stress scale. Both groups demonstrated improvements, except in pulmonary function, with no significant difference between the two groups. Another RCT in Spain targeting patients hospitalized for COVID-19 pneumonia who continued to exhibit symptoms at least three months later, without baseline cardiopulmonary diseases [107]. This trial compared a group that underwent three months

of inspiratory muscle training (IMT) to a non-intervention group, assessing cardiopulmonary exercise tests and quality of life. The IMT group exhibited significant improvements in cardiopulmonary exercise capacity and quality of life. Furthermore, the rehabilitation for post-COVID-19 condition through a supervised exercise intervention trial in Spain targeted 80 patients with mild COVID-19 symptoms persisting for more than three months, without special treatment or baseline cardiopulmonary diseases [108]. Participants were randomly assigned to multicomponent exercise training, IMT, a combination of both methods, or a control group (following WHO self-management recommendations), evaluating dyspnea, fatigue, and cardiopulmonary function after 8 weeks. Supervised exercise programs proved more effective than self-managed rehabilitation according to WHO recommendations, improving dyspnea, fatigue, and depression, and enhanced cardiopulmonary exercise and muscle strength 8 weeks. Additionally, an RCT in Spain involving 88 patients experiencing persistent symptoms such as dyspnea and fatigue three months after COVID-19 diagnosis compared IMT and expiratory muscle training (EMT) between face-to-face and remote rehabilitation groups over 8 weeks, with sessions conducted twice daily (morning/evening, each for 20 minutes), six days a week [109]. Outcome measurements were conducted before the initiation of rehabilitation and at four-week and eight-week intervals after the initiation of rehabilitation. While all groups demonstrated an improvement in quality of life, exercise tolerance did not improve. Inspiratory muscle strength and endurance, as well as lower extremity muscle strength, significantly improved in the face-to-face group, while expiratory muscle strength and maximum expiratory flow improved in the face-to-face EMT group. However, no impact on pulmonary function or psychological state was observed. Similarly, an RCT in Spain for patients with mild COVID-19 symptoms but persistent dyspnea and fatigue for more than three months, divided participants into a professionally supervised group receiving thrice-weekly multicomponent exercise training and a group following WHO self-management recommendations for eight weeks [110]. The professionally supervised multicomponent exercise training group showed improvements in quality of life, fatigue, depression, cardiopulmonary exercise function, and muscle strength. In the UK, a RCT targeting 148 patients with persistent dyspnea symptoms after hospital discharge from COVID-19 allocated participants 4 : 1 to a non-face-to-face IMT group and a non-intervention group for eight weeks [111]. The IMT group showed improvements in dyspnea symptoms and inspiratory muscle strength. Furthermore, another RCT in the UK involving 150 participants with persistent dyspnea at least four weeks post-COVID-19 symptom onset compared a six-week online breathing and wellbeing program (ENO Breathe, using singing for respiratory training) to a non-intervention group [112]. The ENO breathe group demonstrated improvements in mental health composite and dyspnea symptoms. Based on multiple RCT results, respiratory rehabilitation can be actively recommended for treating long COVID. However, the type and duration of rehabilitation treatment should be determined according to the patient's symptoms and accessibility, following the opinion of rehabilitation experts.

6. PREVENTION

(1) What strategies can effectively prevent long COVID?

1) Can antiviral therapy for the treatment of COVID-19 reduce the risk of developing long COVID?

Recommendation
• Antiviral therapy is recommended in the early stages of SARS-CoV-2 infection to prevent long COVID (A, I).

Early administration of antivirals may be beneficial in preventing long COVID. A meta-analysis of observational studies revealed a significant preventive effect (27.5%; 95% CI, 25.3 - 59.1) against the onset of long COVID with early administration of antiviral agents compared to the non-treated group. Furthermore, early antiviral treatment was associated with a decreased risk of hospitalization and death linked to long COVID [146]. While the study by Chilunga et al., included in the meta-analysis, did not demonstrate a statistically significant preventive effect with remdesivir [147], research by Xie et al. indicated that molnupiravir had a significant preventive effect on long COVID [148, 149]. Additionally, three out of four observational studies assessing the effects of nirmatrelvir/ritonavir reported benefits of early antiviral treatment. However, the studies included in the meta-analysis were limited to observational designs, underscoring the necessity for further RCTs to validate these findings. The precise mechanism underlying the preventive effect of early antiviral treatment on long COVID remains uncertain. There is a hypothesis that SARS-CoV-2 virus causes prolonged inflammation in the

body, leading to long COVID [34]. From this perspective, early antiviral treatment may potentially be effective in suppressing viral replication within the body, thereby reducing viral load and ameliorating symptoms associated with COVID-19.

2) Can vaccination to prevent COVID-19 reduce the risk of developing long COVID?

Recommendation
• COVID-19 vaccination is recommended to prevent long COVID (A, I).

Vaccination has shown a preventive effect against long COVID, even in cases of breakthrough infections. A meta-analysis of six observational studies showed that even a single vaccination could demonstrate a significant preventive effect with an OR of 0.539 (95% CI, 0.295 - 0.987) compared with unvaccinated individuals [150]. Other meta-analyses also found a preventive effect, with an OR of 0.64 (95% CI, 0.45 - 0.92) among those who received two primary doses and an OR of 0.60 (95% CI, 0.43 - 0.83) among those who received a single dose [151]. Therefore, COVID-19 vaccination is necessary for long COVID prevention [152, 153]. The mechanism by which COVID-19 vaccination prevents long COVID remains unclear. Theoretically, vaccination could enable rapid elimination of the virus in the body in the event of a breakthrough infection, reduce acute immune responses to lessen tissue damage, and ameliorate dysregulation of the immune system, thereby reducing the risk of secondary autoantibody production. Additionally, both studies qualitatively analyzed the symptom relief effect in patients with long COVID. However, regarding the effect on symptom relief, mixed results were observed, with both positive and negative outcomes, necessitating further quantitative research to draw definitive conclusions.

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Conflict of interest
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Author Contributions
Conceptualization: JWS, EJK, JL, YBS, JYS. Data curation: JWS, EJK, YBS, JYS. Formal analysis: JWS, EJK, YBS, JYS. Funding acquisition: JL. Investigation: JWS, EJK, YBS, JYS. Methodology: EJK, YBS, JYS. Project administration: JWS, EJK, JL, YBS, JYS. Resources: SEK, YK, TK, THK, SHL, EL, YJ, YHJ, YJC. Software: EJK, YBS. Supervision: YBS, JYS. Validation: JWS, EJK. Visualization: JWS, EJK, YBS, JYS. Writing - original draft: JWS, SEK, YK, TK, THK, SHL, EL, YBS, YJ, YHJ, YJC. Writing - review & editing: JWS, EJK, YBS, JYS.

SUPPLEMENTARY MATERIALS

Supplementary Material
Guideline Korean Version

Supplementary Table 1
Recommendations for the diagnosis and treatment of long COVID

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