

Special Article



Clinical Practice Guideline Recommendations for Post-Acute Sequelae of COVID-19

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ABSTRACT

The guidelines presented herewith are based on the “Clinical Practice Guideline Recommendations for Post-Acute Sequelae of COVID-19 (PASC)” published in *Infection & Chemotherapy* in March 2024; these guidelines have been refined by incorporating the most recent Korean and international research findings and clinical evidence published since then. In the context of patients experiencing various physical and mental symptoms that persist long after the acute phase of coronavirus disease 2019 (COVID-19) infection, the diagnosis and management of PASC has emerged as a novel public health challenge. These guidelines are intended to provide standardized diagnostic

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and management recommendations applicable to the Korean healthcare setting and were developed through a comprehensive review of existing guidelines from organizations such as the World Health Organization, the United States National Institutes of Health, the United Kingdom National Institute for Health and Care Excellence, and the European Society of Clinical Microbiology and Infectious Diseases, along with the latest meta-analyses and Korean cohort studies. PASC is defined as the persistent presence of symptoms and signs lasting more than 3 months after COVID-19 diagnosis for which the symptoms cannot be explained by alternative diagnoses. The revised guidelines emphasize the importance of integrated management for patients with PASC, including a multidisciplinary approach considering risk groups, symptom-specific assessment, and rehabilitation and psychological interventions, based on a total of 32 key questions. This revision reflects rapidly evolving research trends regarding the long-term effects of COVID-19 and is expected to serve as an evidence-based standard guideline for future patient care, clinical research, and health policy development in Korea.

Keywords: Long COVID; Post-acute sequelae of COVID-19; Post-acute COVID-19 syndrome; Diagnosis; Management

SUMMARY

1) What are the diagnostic criteria for post-acute sequelae of COVID-19 (PASC)?

Recommendation

- PASC is defined as the persistent presence of symptoms and signs lasting more than 3 months after coronavirus disease 2019 (COVID-19) diagnosis for which the symptoms cannot be explained by alternative diagnoses (G, I).

2) What is the evaluation method for patients with PASC who complain of dyspnea?

Recommendation

- If patients with PASC present with dyspnea, cardiac and pulmonary tests may be considered to assess for the presence of cardiopulmonary disease (B, IIb).

3) What is the evaluation method for patients with PASC who complain of chest pain?

Recommendation

- If chest pain occurs more than 12 weeks after COVID-19 infection, emergency or severe conditions (e.g., cardiovascular disease) should be prioritized for

confirmation or exclusion, and the patient should be referred to the appropriate specialty department as needed (G, IIa).

- Assessment of myocardial injury may entail implementation of electrocardiogram testing and serum troponin analysis. If abnormal findings are detected, echocardiography and cardiac magnetic resonance imaging should be conducted (G, IIa).
- In addition to the cardiovascular system, causes of chest pain may include noncardiac factors such as the chest wall, respiratory system, and gastrointestinal tract; therefore, differential diagnosis should be performed through obtaining medical history and conducting basic examinations (G, IIa).

4) What is the evaluation method for patients with PASC who complain of cough?

Recommendation

- Patients with PASC who present with a cough should undergo a chest X-ray and, if indicated, a chest computed tomography (CT) scan to evaluate for the presence of pulmonary fibrosis or bronchial damage (G, I).
- In accordance with the findings of experts, performance of pulmonary function tests and fractional exhaled nitric oxide testing may be indicated (G, I).

5) What is the evaluation method for patients with PASC who complain of fatigue?

Recommendation

- No singular, specific evaluation test can assess fatigue symptoms in patients with PASC (G, III).
- Fatigue assessment should be conducted through differentiation of physical and mental domains using a multidisciplinary approach, including employment of self-reports and standardized fatigue scales (e.g., Fatigue Severity Scale, Chalder Fatigue Scale, DSQ-SF, and Visual Analogue Scale) (A, IIa).
- A comprehensive medical history, encompassing social and psychological factors, medications, sleep disorders, underlying medical conditions, and COVID-19 sequelae, in conjunction with a physical examination, is essential (G, IIa).
- If indicated, blood tests, electromyography, imaging studies, and functional tests (6-min walk test, tilt test, etc.) should be performed to rule out organic causes (G, IIa).
- This comprehensive approach enables the elimination of organic causes and facilitates the development of customized rehabilitation and management strategies for each patient (G, IIa).

6) What is the evaluation method for patients with PASC who complain of joint and muscle pain?

Recommendation

- Patients who have experienced joint pain or muscle pain for more than 3 months following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may undergo further evaluation; this evaluation may be based on their medical history and physical examination. Additionally, if symptoms persist, a referral to a specialist department may be considered (G, IIb).

7) What is the evaluation method for patients with PASC who complain of headaches?

Recommendation

- Evaluation of headaches associated with PASC should encompass a medical history,

neurological examination, and vital signs (G, I).

- In the absence of neurological red flag signs, management of this condition should align with the standard protocol for primary headache disorders (G, I).
- In instances where a differential diagnosis of secondary headaches is required, implementing brain imaging studies and referring patients to a neurologist for specialized evaluation and treatment is advised (G, I).

8) What is the evaluation method for patients with PASC who complain of cognitive impairment or brain fog (concentration or attention deficit)?

Recommendation

- In patients exhibiting cognitive impairment or brain fog (concentration or attention deficit), potential causes such as psychiatric disorders, sleep disorders, medication-associated adverse events, and endocrine, autoimmune, or infectious diseases should be evaluated through detailed medical history taking, neurological examination, and neuropsychological testing (G, I).
- In cases where local neurological abnormalities or brain lesions are suspected, imaging studies, including brain magnetic resonance imaging, should be performed (G, I).
- For cognitive impairment lasting over 3 months or causing functional disability in daily life, work, or studies, cognitive screening tests such as Montreal Cognitive Assessment and Symbol Digit Modalities Test should be administered. If indicated, a multifaceted assessment including neuropsychological testing, sleep evaluation, and quality of life assessment (EQ-5D-5L, Barthel Index, etc.) should be considered.
- For persistent cognitive impairment or attention deficits, referral to a specialist such as a cognitive rehabilitation specialist or psychiatrist should be considered (G, IIa).

9) What is the evaluation method for patients with PASC who complain of anxiety or depression?

Recommendation

- In cases of severe psychiatric symptoms or risk of self-harm or suicide, immediate referral for psychiatric evaluation and treatment is recommended (G, I).
- A referral to a psychiatrist is recommended to rule out the presence of psychiatric disorders that could explain

depression or anxiety (G, I).

- During the assessment process, a wide range of potential mental health conditions, including depression, anxiety, post-traumatic stress disorder, and adjustment disorder should be considered. A comprehensive, multifaceted evaluation is recommended, including an analysis of their psychiatric history, family history, social support networks, and suicide risk (G, I).
- The Hospital Anxiety and Depression Scale and the Patient Health Questionnaire-9 can be used as screening tools; however, clinical evaluation is recommended in conjunction with these tools for diagnosis (G, I).
- Early identification of high-risk groups by evaluating major risk factors (such as female sex, prior psychiatric history, acute-phase inflammation, uncertain recovery, and cognitive impairment) should be considered (G, IIa).

10) What is the evaluation method for patients with PASC who complain of sleep disorders?

Recommendation

- A review of sleep patterns and assessment of factors interfering with sleep (habits, substances, and environment) as well as underlying conditions such as sleep apnea, restless legs syndrome, pain, and anxiety is recommended (G, I).
- For differential diagnosis and evaluation of complex symptoms, a referral to a sleep medicine specialist or psychiatrist should be considered (G, IIa).
- A multifaceted approach may be considered during diagnosis, utilizing screening tools such as the Insomnia Severity Index), sleep history and sleep diaries, and objective assessment tools such as actigraphy if indicated (G, IIb).

11) What is the evaluation method for patients with PASC who complain of swallowing disorders (dysphagia)?

Recommendation

- For diagnosis of PASC-related swallowing disorders, a video fluoroscopic swallowing study or fiberoptic endoscopic examination of swallowing may be performed, and referral to a specialist in swallowing disorders is recommended (G, I).

12) What is the evaluation method for patients with PASC who complain of olfactory or gustatory disorders (anosmia, hyposmia, or dysgeusia)?

Recommendation

- If patients with PASC present with olfactory or gustatory disorders, other organic causes may be ruled out first; no primary assessment tool is recommended for evaluating olfactory or gustatory disorders (G, IIb).

13) What is the evaluation method for patients with PASC who complain of post-exercise malaise (PEM)/post-exertional symptom exacerbation (PESE)?

Recommendation

- If patients with PASC present with post-exertional symptoms or functional limitations, assessment of such abnormalities may be conducted through the utilization of questionnaires, with cardiopulmonary exercise testing serving as the confirmatory test (G, IIb).

14) What is the evaluation method for patients with PASC who complain of postural tachycardia syndrome (POTS)?

Recommendation

- If patients with PASC present with tachycardia upon posture change, the NASA Lean Test or head-up tilt test may be considered (G, IIb).

15) How is dyspnea treated in patients with PASC?

Recommendation

- Current evidence does not support recommending specific pharmacologic therapies for the treatment of dyspnea in patients with PASC (A, I).
- Respiratory rehabilitation is recommended for patients with PASC who have persistent respiratory symptoms or functional impairment, to improve respiratory symptoms and overall functional capacity (A, I).

16) How is a cough treated in patients with PASC?

Recommendation

- Insufficient evidence exists to recommend specific pharmacological therapy for cough symptoms in patients with PASC. However, according to Korean chronic cough treatment guidelines, empirical treatment with antihistamines or inhaled corticosteroids may be considered for symptom control. Nonetheless, evidence supporting this approach is also limited, and its clinical application may be carefully considered (G, IIb).

17) How is fatigue treated in patients with PASC?

Recommendation

- In the event that neurological or musculoskeletal abnormalities are identified during evaluation of patients presenting with fatigue, consultation with the relevant specialty is recommended. In the absence of an identifiable organic cause, rehabilitation therapies, including exercise and breathing training, physical therapy, and occupational therapy, may be considered as therapeutic interventions (G, IIb).
- Currently, limited evidence is available for treating fatigue in patients with PASC; however, standardized rehabilitation programs may help improve symptoms. Some adjunctive therapies and medications have demonstrated potential efficacy, but further large-scale studies are warranted (G, IIb).

18) How is joint and muscle pain treated in patients with PASC?

Recommendation

- Treatment of joint and muscle pain associated with PASC in patients more than 3 months post-onset of COVID-19 should be initiated with the implementation of general pain management guidelines, which are contingent upon the nature of the pain and the accompanying symptoms (G, IIa).
- In patients with post-onset COVID-19 presenting with fibromyalgia-like symptoms, including widespread pain, fatigue, and functional impairment, transcutaneous

electrical nerve stimulation may be considered as an adjunctive therapy (A, IIb).

19) How are headaches treated in patients with PASC?

Recommendation

- For headaches associated with PASC, symptomatic treatment may be considered as for primary headaches after excluding organic causes. In cases where migraine symptoms are persistent and result in significant disruption to daily life, preventive migraine treatment may be indicated (G, IIb).

20) How is cognitive impairment or brain fog (concentration or attention deficit) treated in patients with PASC?

Recommendation

- If objective cognitive decline is identified on cognitive screening tests or if symptoms of cognitive impairment or brain fog persist, potential causative factors should be evaluated. These factors may include medication-associated adverse events, neurological disorders, mood disorders, sleep disorders, or endocrine, autoimmune, or infectious diseases. In the event that any such condition is suspected, the patient should be referred to the relevant specialty department (G, I).
- For patients exhibiting symptoms of concentration or attention deficits and cognitive impairment, consideration should be given to referral for evaluation by a cognitive rehabilitation specialist or psychiatrist and subsequent enrollment in cognitive rehabilitation therapy (G, IIa).
- Non-pharmacological treatments may include education and self-management training, as well as cognitive training (attention training, metacognitive strategies, etc.); if indicated, these may be combined with multidisciplinary rehabilitation programs (G, IIb).
- Lifestyle modifications (adequate sleep, balanced nutrition, medication reevaluation) and tailored aerobic and cognitive stimulation exercise programs are recommended. For some patients, the use of repetitive transcranial magnetic stimulation as an adjunctive

treatment may be considered (G, IIb).

- Low-dose naltrexone and the Biosound Therapy System may be considered only in selected cases or specialized settings, given the paucity of evidence supporting their use (C, IIb).

21) How is anxiety or depression treated in patients with PASC?

Recommendation

- In cases of severe psychiatric symptoms or risk of self-harm or suicide, immediate referral for psychiatric evaluation and treatment is recommended (G, I).
- A consultation with a psychiatrist is advised in the presence of an indication of a psychiatric disorder that could explain the occurrence of depression or anxiety (G, I).
- For depressive symptoms in patients with PASC, administration of a selective serotonin reuptake inhibitor may be considered a therapeutic option (C, IIb).
- Antidepressants are not recommended for adjustment disorders. Anxiety disorders can be treated with self-management, short-term medication, and psychotherapy. If indicated, a psychiatric consultation and a multidisciplinary team approach should be considered (G, IIa).
- Peer support, the utilization of social support networks, and suicide risk assessment employing the risk-urgency-danger approach may also be regarded as useful adjunct strategies (G, IIb).

22) How are sleep disorders treated in patients with PASC?

Recommendation

- Recommended treatment for sleep disorders includes sleep hygiene correction, elimination of interfering factors (habits, substances, and environment), and treatment of underlying conditions such as sleep apnea, restless legs syndrome, pain, and anxiety (G, I).
- For first-line treatment, cognitive behavioral therapy for insomnia, use of a sleep diary and the administration of short-term medication may be considered if indicated. In the absence of a response or the presence of complex issues, referral to a

sleep medicine or mental health specialist should be considered (G, IIa).

23) How are swallowing disorders (dysphagia) treated in patients with PASC?

Recommendation

- In treating PASC-associated dysphagia, swallowing rehabilitation exercises, neuromuscular stimulation therapy, and nutritional status improvement may be attempted. Referral to a specialist in dysphagia is recommended (G, I).

24) How are olfactory or gustatory disorders treated in patients with PASC?

Recommendation

- Olfactory training has demonstrated efficacy in ameliorating olfactory dysfunction in patients with PASC, to date, no evidence supports pharmacological therapy (A, I).
- Clinical application of palmitoylethanolamide (PEA) and topical corticosteroid nasal sprays may be considered with caution as adjunctive options in selected patients, as only limited and inconsistent evidence supports their use (G, IIb).

25) How is PEM/ PESE treated in patients with PASC?

Recommendation

- In patients with PASC presenting with PEM, education on maintaining appropriate rest and activity cycles, including pacing and symptom-titrated activity while avoiding graded exercise programs that may exacerbate symptoms, may be considered (G, IIb).

26) How is POTS treated in patients with PASC?

Recommendation

- Non-pharmacological therapies and pharmacological

therapies may be considered for patients with PASC who present with autonomic nervous system dysfunction, depending on their hemodynamic status (G, IIb).

27) Should prophylactic anticoagulants be administered to patients with PASC?

Recommendation

- Insufficient evidence is available to recommend or not recommend administering anticoagulants or antiplatelet agents to patients with PASC for the purpose of preventing thrombosis. The decision to prevent thrombosis in patients with PASC should be tailored to the patient's specific condition, considering both the probability of thrombosis and the risk of bleeding. However, the administration of therapeutic-dose anticoagulants or antiplatelet agents for the purpose of preventing blood clots is not endorsed. In instances where patients present with dyspnea without any discernible pulmonary lesions, diagnostic procedures should be conducted to differentiate between pulmonary artery thrombosis and deep vein thrombosis. If thrombus is diagnosed, the decision to administer anticoagulants or antiplatelet agents should be made according to relevant guidelines (C, III).

28) Should systemic steroids be administered to patients with PASC?

Recommendation

Systemic steroids

- The use of systemic steroids is not advised for the purpose of preventing subsequent PASC during the acute phase of COVID-19 (G, III).
- The current body of evidence does not support the recommendation of systemic steroids for PASC. The use of systemic steroids is not recommended in the absence of specific indications (D, III).

Topical steroids - Inhaled or intranasal administration

- In the absence of clear indications such as bronchial hyperresponsiveness, inhaled steroids

are not recommended for chronic cough following COVID-19 infection, and their clinical application should be considered with caution (D, III).

- The use of intranasal steroids for the purpose of improving diminished olfactory function is not recommended in patients with PASC in the absence of indications from other diseases (G, III).

29) Should anti-fibrotic drugs be administered to patients with PASC?

Recommendation

- The treatment of PASC-associated pulmonary fibrosis involves the use of diagnostic procedures such as chest CT, which provide crucial information to evaluate the extent of pulmonary fibrosis (A, I).
- In patients with severe COVID-19 and confirmed pulmonary fibrosis, antifibrotic agents (pirfenidone or nintedanib) are recommended, after appropriate radiologic confirmation and assessment of comorbidities (A, I).
- The selection of antifibrotic agents should be based on a comprehensive evaluation of the underlying lung disease, and this decision should be made in consultation with a pulmonologist (A, I).

30) Is respiratory rehabilitation therapy necessary for patients with PASC?

Recommendation

- Numerous randomized controlled trials (RCTs) have indicated that general respiratory rehabilitation therapy in patients with PASC is beneficial for treating various symptoms of PASC, thus recommending general rehabilitation/respiratory rehabilitation therapy (A, I).

31) Can antiviral treatment administered for the purpose of treating COVID-19 reduce risk of developing PASC?

Recommendation

- Early antiviral treatment in the initial phase of SARS-CoV-2 infection may help reduce the risk of

developing PASC and the resulting hospitalization and death (B, I).

- Use of antiviral drugs for treatment purposes for the management of patients with PASC is not recommended (A, I).

32) Can COVID-19 vaccination reduce the risk of developing PASC?

Recommendation

- COVID-19 vaccination is recommended to reduce the risk of developing PASC (A, I).

1. BACKGROUND AND PURPOSE OF THE GUIDELINES

As of September 2025, the global health crisis posed by COVID-19 persists. Given the widespread scaling back of diagnostic and reporting systems in most countries since the pandemic, accurate ascertainment of the global cumulative number of confirmed cases is challenging. However, as estimated by the World Health Organization (WHO), a considerable proportion of the global population has been infected with the SARS-CoV-2 virus at least once. Among these, some individuals continue to report various physical and mental symptoms for months or longer following acute SARS-CoV-2 infection, which is referred to as Post-Acute Sequelae of SARS-CoV-2 (PASC). The majority of patients diagnosed with COVID-19 experience mild symptoms and make a full recovery; however, a significant proportion of patients develop long-term sequelae that affect multiple organs, including fatigue, shortness of breath, cognitive impairment, pain, sleep disorders, and psychoneurological symptoms. The pathophysiology and mechanisms underlying these symptoms remain to be fully elucidated. The absence of internationally unified diagnostic criteria and the paucity of evidence to determine which tests should be performed and which treatments are appropriate are salient issues in this field. Consequently, the prevailing paradigm in clinical practice has been predicated on the experiential wisdom and clinical acumen of individual clinicians.

In response to the need to establish clinical standards grounded in a consensus among experts in the field

and the most recent evidence, the Korean Society of Infectious Diseases (KSID) unveiled the "Preliminary Clinical Practice Guideline Recommendations for Post-Acute Sequelae of COVID-19 (PASC)" in September 2022. The dearth of research evidence at the time rendered the establishment of conventional evidence-based guidelines based on systematic literature reviews a challenging endeavor. Consequently, the preliminary recommendations were presented as practical, rapid guidelines, developed based on the limited evidence available at the time and expert opinion. Approximately one year later, in March 2024, as numerous Korean and international studies accumulated and deepened understanding of the pathophysiology, risk factors, clinical manifestations, and treatment approaches, the Korean Society for Infectious Diseases reorganized its existing recommendations based on evidence and published the "Clinical Practice Guideline Recommendations for Post-Acute Sequelae of COVID-19 (PASC)" in *Infection & Chemotherapy*. This revision updates the 2024 guidelines by incorporating the latest research findings published since then, resulting in a set of revised evidence-based clinical practice guidelines. These guidelines were systematically developed to present fundamental principles for the diagnosis, evaluation, treatment, and management of patients with PASC. The overarching objective of these guidelines is to establish a framework for multidisciplinary collaboration involving infectious disease, respiratory medicine, neurology, physical medicine and rehabilitation, and psychiatry; the primary aim is to assist clinicians in making care decisions that are tailored to each patient's individual circumstances. Moreover, the guidelines seek to support the development of a patient-centered integrated care system and may be used for personal medical treatment and educational purposes. However, their application for commercial use or for the purposes of review and evaluation is strictly prohibited. For any other purpose, written approval from the Long COVID research group of KSID must be obtained.

2. METHODS

(1) Composition of the guideline development committees

As part of the research project on the sequelae of COVID-19 by the Korea Disease Control and Prevention Agency (KDCA), KSID established the Post-Acute Sequelae of COVID-19 Treatment Guideline Steering Committee. The Clinical Practice Guideline Working

Committee consisted of 13 experts representing the fields of infectious diseases, respiratory medicine, cardiology, neurology, and psychiatry.

(2) Guideline development process

A substantial body of clinical guidelines pertaining to PASC has been disseminated by prominent nations and international organizations. The existing guidelines underwent a systematic review and adaptation for the development of these guidelines. Furthermore, recent research findings have been incorporated to ensure that these guidelines reflect the most recent scientific evidence available.

1) Search data source

The comprehensive literature search was conducted using the PubMed and EMBASE databases. Manual searches were also conducted to supplement any omitted studies. Preprint databases (such as MedRxiv) were excluded from the search.

2) Search strategy

The development of the comprehensive search strategy was primarily executed using the PubMed database, with search terms derived from recommendations made by committee members. These recommendations were based on predefined research questions and the known specific symptomatology of PASC. A preliminary search was conducted, and the ensuing results were then reviewed and discussed to incorporate additional feedback and revisions.

The final search terms included core expressions of PASC such as “long COVID,” “post-COVID,” and “after COVID,” in combination with symptom-related keywords including dyspnea, cough, chest pain, fatigue, myalgia, headache, depression, brain fog, sleep disorder, dysphagia, ageusia, anosmia, post-exertional malaise, orthostatic intolerance, and biomarker.

Database searches were conducted on all selected platforms for the period from July 1, 2023, to April 30, 2025, according to the established search protocol.

3) Literature selection criteria

The inclusion and exclusion criteria for each clinical question were established based on the Population, Intervention, Comparison, and Outcomes framework, as well as the specific study design. These criteria were

finalized through discussions among the members of the Working Committee.

The inclusion criteria were as follows: ① clinical studies reporting patient numbers and clinical characteristics related to PASC, ② studies clearly presenting MeSH terms or keywords to describe research methodology, and ③ studies published in English.

The exclusion criteria were as follows: ① case reports, ② studies lacking statistical data or tabulated results, and ③ gray literature such as conference abstracts, theses, and proposal papers.

The methodological rigor of the included studies was assessed by evaluating the risk of bias and overall study quality for each study using validated assessment tools appropriate for the respective study design. Each study was subjected to independent review by two investigators, and any discrepancies in the assessment results were resolved through consultation with subject matter experts.

4) Assessment of risk of bias in selected literature

The quality of the studies finally included in the review was assessed by applying appraisal instruments suitable for each study design. Each study was independently evaluated by at least two investigators, and inter-rater discrepancies were resolved through expert consultation to ensure methodological rigor and consensus.

- Quality assessment tool for the evaluation of guidelines: AGREE II (Appraisal of Guidelines Research and Evaluation II)

AGREE II is recognized as the most widely used assessment tool on a global scale and was thus utilized as the primary method for evaluating the methodological quality of clinical practice guidelines. It evaluates six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each domain is evaluated independently, and the resulting scores are not combined to produce a single composite score. To ensure reliability, each item of AGREE II was assessed by at least two independent evaluators using a 7-point Likert scale.

- Quality assessment tools for systematic literature reviews and meta-analyses: Scottish Intercollegiate Guidelines Network (SIGN)

The SIGN checklist was used for systematic literature reviews and meta-analysis studies. This tool includes a total of 10 items related to the study design, including the clarity of the research question, randomization, allocation concealment, blinding, baseline comparability, intention-to-treat analysis, outcome reporting, attrition rates, and homogeneity of institutions and individuals. This checklist is designed to facilitate a systematic evaluation of the methodological quality of RCTs incorporated into secondary analyses.

- Quality assessment tool for RCTs: Joanna Briggs Institute (JBI) checklist

The JBI checklist was applied in the context of the primary study, which was designed as a randomized controlled trial. This tool includes eight items: participant selection criteria, description of inclusion and exclusion criteria, assessment of exposure and disease status, accuracy of disease diagnosis, control of confounding variables, validity of outcome variable measurement, and statistical appropriateness of the applied statistical analysis. Each item was scored as one point for “yes,” and zero points for “unclear,” “no,” or “not applicable,” enabling standardized scoring among independent evaluators.

5) Level of evidence and strength of recommendation

The literature and extant guidelines that were utilized as evidence for the draft recommendations were classified by the Working Committee into four distinct levels of evidence based on predefined assessment criteria (Table 1).

The strength of recommendation was determined according to the modified Grading of Recommendations Assessment, Development, and Evaluation system. In this process, the Working Committee applied the classification system by comprehensively considering the level of evidence, potential benefits and harms, and the feasibility of implementation (Table 2).

For some recommendations, when user survey results demonstrated clear clinical benefits or high practicality, their strength of recommendation was elevated through deliberation by the Working Committee and Writing Committee, even if their level of evidence was low.

(3) Development based on evidence-based consensus

These guidelines were developed using an adaptation methodology based on previously developed KSID guidelines. To ensure the latest evidence was reflected, all panel members were provided with electronic copies of the literature selected through a systematic search. Each panel member was responsible for key questions regarding the overview, diagnosis, treatment, and prevention of 12 specific clinical manifestations associated with PASC and drafted recommendations on these topics. The drafting process involved iterative review and consensus-building through electronic communication, virtual meetings, and in-person discussions. After thorough discussion, the final guidelines were approved with unanimous endorsement

Table 1. Level of evidence [1]

Level of evidence	Definition
A	A clear basis for recommendation is evident. At least one randomized controlled trial, meta-analysis, or systematic literature review study is available.
B	A reliable basis for recommendation is present. At least one well-conducted non-randomized clinical study, such as a case-control study or cohort study, is available.
C	A basis for recommendation is present, but it is unreliable. Only low-level relevant evidence, such as observational studies and case reports, is available.
D	The basis for deriving the recommendation is expert opinion grounded in clinical experience and expertise.
G	The basis for deriving the recommendation is high-quality clinical practice guidelines.

Table 2. Strength of recommendation [1]

Strength of recommendation	Definition	Notation
Class I	The level of evidence (A) and benefits are clear, with high utility in clinical practice.	Recommended
Class IIa	The level of evidence (B) and benefits are reliable, with high or moderate utility in clinical practice.	Should be considered
Class IIb	Although the level of evidence (C or D) and benefits are unreliable, it has high or moderate utility in clinical practice.	May be considered
Class III	The level of evidence (C or D) is unreliable, with potential for harm, and it has low utility in clinical practice.	Not recommended

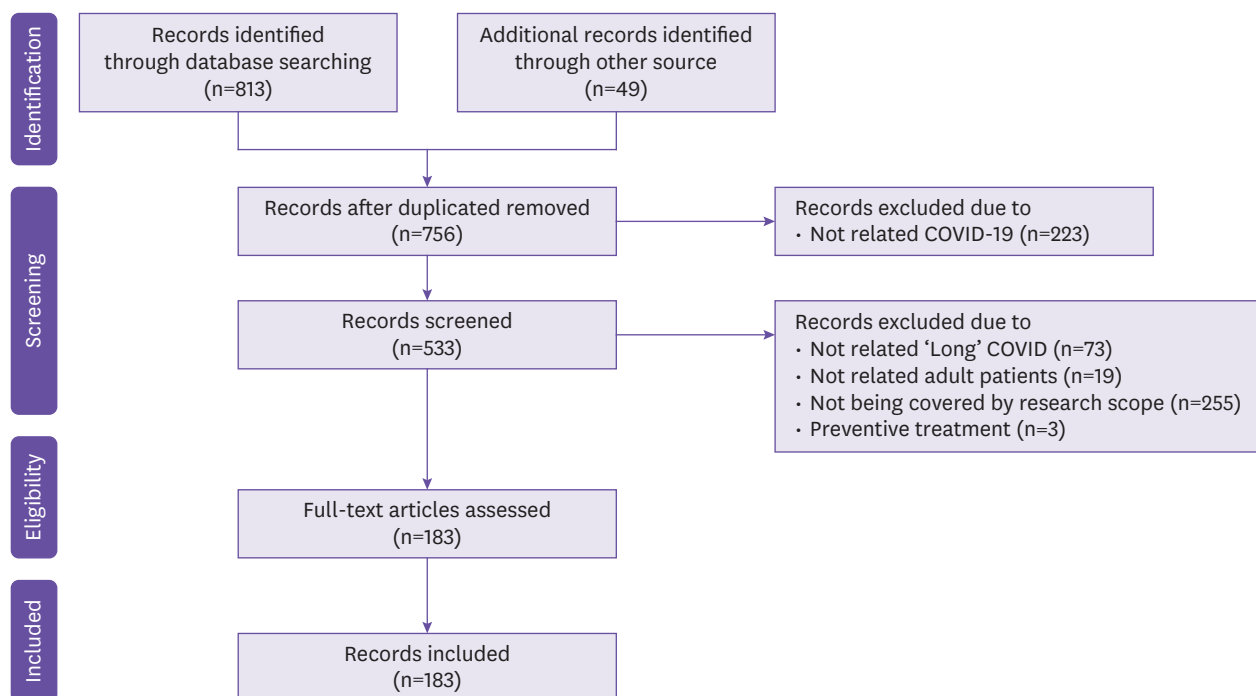


Figure 1. Flowchart of the selection process for clinical practice guidelines subject to quality assessment (PRISMA flow chart).

by all panel members. Furthermore, opinions from external experts were incorporated through peer review, followed by a critical review by the entire committee. The final version reflected matters deemed necessary (Fig. 1).

3. OVERVIEW

(1) What is the definition of PASC?

The various symptoms or signs of COVID-19 commonly persist for up to 4 weeks after diagnosis, which is referred to as acute COVID-19. The definition of PASC, frequently referred to as long COVID, exhibits slight variations in terminology and definition across various institutions and guidelines. Nevertheless, the WHO definition is widely accepted as the prevailing standard. The WHO defines post-COVID-19 condition as a set of symptoms or signs that manifest during or after the acute phase of COVID-19, cannot be explained by other diagnoses, and persist for more than 2 months or 12 weeks after diagnosis [2]. Other relevant 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." The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines define ongoing symptomatic COVID-19 as the persistence of symptoms or signs that began during the acute phase of COVID-19 or later, improving within four to 12 weeks of diagnosis. Cases persisting beyond 12 weeks are defined as post-COVID-19 syndrome [3]. In contrast, the United States National Institutes of Health (NIH) refers to cases where

PubMed

#1: COVID-19 OR "COVID 19"
[MeSH Terms] OR COVID-2019 OR SARS-CoV-2 OR 2019-nCoV OR 2019-SARS-CoV-2: 1,716 studies

#2: survivor* OR recover* OR persistent OR follow up
OR discharge* OR sequela* OR long COVID: 11,428 studies

#3: ("long term" AND follow up) OR 1 year OR one year
OR 12 months OR twelve months OR after OR post:
21,337 studies

#4: ((long COVID) OR (post covid)) OR (after covid))
AND ("each symptoms"[All Fields])

#5: #1 AND #2 AND #3 AND #4

Filters: Abstract, Meta-Analysis, Randomized, Cohort

Controlled Trial, Review, Systematic Review, Humans,
English, from 2023.7.1. to 2025.4.30: 813 studies

symptoms or signs persist 4 weeks after COVID-19 diagnosis as post-acute sequelae of SARS-CoV-2 infection [4]. Despite the paucity of evidence for particular pathophysiological changes at the 12-week stage of the disease, standardization of terminology appears indispensable for the advancement of research and clinical trials concerning post-acute sequelae of COVID-19. Therefore, these guidelines define symptoms or signs occurring during the acute phase or thereafter that cannot be explained by other conditions and persist within 4-12 weeks of COVID-19 diagnosis as “post-acute COVID-19” and those persisting beyond 12 weeks as “post-acute sequelae of COVID-19 [1].

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

PASC can occur across all age demographics and is associated with the severity of the acute illness, although instances have been observed in patients with mild disease as well. The highest diagnosis rate is observed among individuals aged 36-50 years, and the majority of PASC cases are characterized by mild, non-hospitalized cases of COVID-19 [5].

The incidence rate varies by variant, with 10.8% for Delta variant infections and 4.5% for Omicron variant infections, indicating a lower reported incidence of PASC in Omicron variant infections. Based on WHO definition criteria, the estimated incidence of PASC due to Omicron variant infection is 11% [6].

A recent study conducted in Australia estimates the prevalence of PASC in symptomatic adult COVID-19 patients to be within the range of 0.17%-4.4%. The prevalence rate was lower among adults infected with the Omicron variant who had been vaccinated: 0.09% among non-hospitalized adults and 1.9% among hospitalized adults. The prevalence rate of PASC among children and adolescents was found to be approximately 3.7%, with non-hospitalized children at 1.7% and hospitalized children at up to 5.2% [7].

While PASC typically resolves over time [3], with an average duration of 4 months in non-hospitalized patients and 9 months in hospitalized patients [8], a meta-analysis involving over 1.28 million COVID-19 survivors from 32 countries has identified that 49% of patients experience at least one symptom of PASC within 12 months post-infection [9]. A follow-up study of Korean adult PASC patients further validated the persistent

presence of PASC in 48.8-52.7% of them approximately 12 months post-infection [10, 11]. A prospective cohort study of PASC conducted at six tertiary hospitals in Korea identified PASC in 54.5% of patients within 6 months and in 34.6% of patients at 18 months [12].

Risk factors associated with the occurrence of PASC may include female sex, advanced age, high body mass index, smoking history, underlying medical conditions (anxiety or depression, asthma, chronic obstructive pulmonary disease, hypertension, diabetes, dyslipidemia, ischemic heart disease), and severe COVID-19 (requiring hospitalization or intensive care unit [ICU] admission). However, the association of these risk factors varies depending on the specific PASC symptom, as demonstrated in various studies [13]. Females have a PASC risk that is twice as high as that of males [3]. Furthermore, evidence substantiates that females are more prone to developing neuropsychiatric PASC than males [14, 15].

The prevalence of PASC in Korea according to WHO criteria was 19.7-24.9% in females, while the prevalence of PASC was 12.7% in males. The risk of developing PASC was higher in females (odds ratio [OR], 2.43; 95% confidence interval [CI], 1.53-3.87) and in patients with underlying conditions (OR, 1.81; 95% CI, 1.24-2.64) [16].

Severe COVID-19 has demonstrated a strong association with fatigue [3]. COVID-19 vaccination and early antiviral use are associated with a reduced risk of developing PASC [13, 17, 18]. However, even among individuals who have received two or more COVID-19 vaccine doses, the risk of neurological, psychiatric, musculoskeletal, and respiratory PASC is known to increase with each additional reinfection [19].

(3) What are the clinical features, pathophysiology, and mechanisms of PASC?

Following acute SARS-CoV-2 infection, the majority of patients show improvement in symptoms. However, approximately 15% of patients, including severe cases, may develop clinical sequelae after chronic organ damage or exhibit symptoms of PASC [20]. PASC may occur after recovery from acute COVID-19 symptoms, may persist from the acute phase, and may fluctuate or recur over time [2]. The duration of recovery varies among individuals, but the majority of patients demonstrate

improvement within approximately 12 weeks [3]. PASC is also associated with a decline in quality of life [10, 14] and is characterized by the absence of specific diagnostic tests or effective treatments to date. The United States Centers for Disease Control and Prevention report that one in five COVID-19 survivors aged 18–64 years and one in four survivors aged 65 years and older may experience persistent sequelae after COVID-19, which can manifest in over 200 different symptoms or signs, including fever, dyspnea, cough, chest pain, palpitations, tachycardia, abdominal pain, diarrhea, headache, dizziness, sensory abnormalities, smell abnormalities, taste abnormalities, pain, fatigue, PEM, joint pain, muscle pain, cognitive impairment, insomnia, depression, anxiety, post-traumatic stress disorder (PTSD), menstrual irregularities, erectile dysfunction, hair loss, and thirst.

The pathophysiology and mechanisms of PASC include immune dysregulation, microbiome dysbiosis, autoimmunity, blood clotting and endothelial abnormalities, and dysfunctional neurological signaling caused by persistent SARS-CoV-2 virus or reactivation of other viruses such as Epstein-Barr virus (EBV) or human herpesvirus-6 [5]. A United Kingdom biobank study comparing brain imaging before and after infection has also confirmed reduced brain parenchymal volume, tissue damage, and cognitive decline [21]. Furthermore, a follow-up study tracking 9,764 participants (including both SARS-CoV-2 infected and non-infected individuals) from the United States RECOVER study of an adult cohort for up to 6 months post-SARS-CoV-2 infection demonstrated a higher prevalence of PEM (87.3%), fatigue (85.3%), brain fog (63.7%), dizziness (62.4%), gastrointestinal symptoms (59.3%), and heart palpitations (57.1%) [22]. Brain fog symptoms include concentration and memory deficits, as well as cognitive decline. A study examining the prevalence of PASC up to two years after SARS-CoV-2 infection in Korean patients confirmed that neurological and psychiatric symptoms, such as fatigue (34.8%), memory deficits (30.3%), concentration deficits (24.2%), insomnia (20.5%), and depression (19.7%), could persist at a higher frequency over an extended period compared with other symptoms [22]. A comparative study of hospitalized and non-hospitalized patients two years after SARS-CoV-2 infection revealed that memory deficits were observed in 20% of the hospitalized group and 15.9% of the non-hospitalized group. However, no statistically significant difference was observed between the two groups [23]. Memory deficits were observed in 28% of patients, while concentration deficits were

observed in 20% of patients following infection with the Omicron variant [6]. Of note, memory deficits were identified in 1.3% of patients with PASC who had been infected (median age, 34 years) [24]. A study using data from the National Health Insurance Service found that the incidence of dementia among COVID-19 survivors was 1.39 times higher than in the control group [25]. A multitude of studies have continued to report associations between SARS-CoV-2 viral infection and cognitive decline [26, 27]. Long-term follow up is warranted, particularly with respect to the heightened risk of neurodegenerative diseases associated with PASC-related symptoms.

4. DIAGNOSIS

(1) What are the diagnostic criteria for PASC?

Recommendation

- PASC is defined as the persistent presence of symptoms and signs lasting more than 3 months after a COVID-19 diagnosis for which the symptoms cannot be explained by alternative diagnoses (G, I).

These clinical practice guidelines define PASC as the persistent presence of symptoms and signs lasting more than 3 months after a COVID-19 diagnosis, for which the symptoms cannot be explained by alternative diagnoses (G, I). The United States NIH has proposed a standardized symptom-based diagnostic framework for PASC [22]. This diagnostic framework employs a scale ranging from 1 to 8 points to assign differential weights to each of the 12 primary symptoms of PASC (PEM, fatigue, brain fog, dizziness, gastrointestinal symptoms, palpitations, changes in sexual desire or function, olfactory or gustatory dysfunction, thirst, chronic cough, chest pain, and abnormal movements). The presence of PASC was determined by a total score of 12 points or higher. The developed diagnostic framework was subsequently applied to 2,231 individuals (early Omicron wave infections) who were first infected after December 1, 2021, and registered within 30 days. At the 6-month mark, 10% of these individuals were confirmed to have PASC. This was lower than the rates observed in individuals infected before the emergence of the Omicron variant (35.4%) or during the later stages of the Omicron wave (16.6%), suggesting that the timing of viral infection, vaccination

Table 3. Scoring by the Korean symptom-based diagnostic framework for PASC

Symptom	Regression coefficient	Score
Fatigue	0.925	9
Olfactory or gustatory dysfunction	0.517	5
Palpitations	0.452	5
Concentration deficits	0.349	3
Skin rash	0.298	3
Muscle weakness	0.250	2
Chest pain	0.221	2
Menstrual cycle changes	0.186	2
Cough	0.089	1

status, and reinfection status significantly influence the development of PASC.

The National Institute of Infectious Diseases under the KDCA also developed a symptom-based diagnostic framework for PASC by applying logistic lasso regression analysis using the Korean PASC cohort in a manner similar to that of the United States NIH (unpublished data). PASC was defined as a score of 13 or higher, calculated by summing the scores assigned to nine symptoms—including fatigue, olfactory or gustatory dysfunction, palpitations, concentration deficits, skin rash, muscle weakness, chest pain, menstrual cycle changes, and cough—each scored on a differentially weighted scale from 1 to 9 (Table 3). Applying these criteria, 18% of COVID-19 patients were classified as having PASC.

(2) What diagnostic tests can be performed based on the clinical manifestations of patients with PASC?

1) What is the evaluation method for patients with PASC who complain of dyspnea?

Recommendation

- If patients with PASC present with dyspnea, cardiac and pulmonary tests may be considered to assess for the presence of cardiopulmonary disease (B, IIb).

A systematic literature review and meta-analysis of the prevalence and risk factors for persistent dyspnea after COVID-19 revealed a significant decrease in dyspnea symptoms between 1–6 and 7–12 months post-infection, with a prevalence of 26% (95% CI, 23–29). In cases of severe or critical acute infection at admission,

reports of dyspnea were more frequent in females, and reports for Asian patients were fewer than those for European or North American patients [28]. The United States multidisciplinary clinical practice guidelines for post-COVID-19 cardiac complications and treatment recommend echocardiography and B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) testing for patients with persistent dyspnea to differentiate from cardiac disease [2]. Furthermore, multicenter prospective observational studies have suggested that plain chest X-rays and chest CT scans are not related to dyspnea symptoms but are necessary to differentiate other pulmonary parenchymal diseases from pulmonary fibrosis. Pulmonary function tests, including diffusion capacity, the 6-min walk test, and cardiopulmonary exercise testing (CPET), may be associated with dyspnea and are related to initial severity [29, 30]. A systematic review and meta-analysis of 38 studies (a total of 2,160 participants) on cardiopulmonary exercise testing found that patients with persistent PASC symptoms had mean maximum oxygen uptake that was 4.9 mL/kg/min lower, albeit with low-quality evidence [31]. However, CPET was suggested to be useful in narrowing down the differential diagnosis of dyspnea on exertion.

A systematic literature review or meta-analysis specifically evaluating persistent dyspnea following COVID-19 is currently lacking. Furthermore, guidelines from various countries offer differing recommendations for assessing dyspnea. Consequently, assessment is recommended based on expert opinion, and new evidence may be incorporated as it emerges from future research.

2) What is the evaluation method for patients with PASC who complain of chest pain?

Recommendation

- If chest pain occurs more than 12 weeks after SARS-CoV-2 infection, emergency or severe conditions (e.g., cardiovascular disease) should be prioritized for confirmation or exclusion, and the patient should be referred to the appropriate specialty department as needed (G, IIa).
- Assessment of myocardial injury may entail the implementation of electrocardiogram testing and serum troponin analysis. If abnormal findings are detected, echocardiography and cardiac magnetic

resonance imaging should be conducted (G, IIa).

- In addition to the cardiovascular system, causes of chest pain may include noncardiac factors such as the chest wall, respiratory system, and gastrointestinal tract, in addition to the cardiovascular system; therefore, differential diagnosis should be performed through obtaining medical history and conducting basic examinations (G, IIa).

Persistent chest pain has been reported in approximately 10–20% of patients 30–60 days after acute SARS-CoV-2 infection [32]. For patients presenting with chest pain more than 12 weeks after acute SARS-CoV-2 infection, an appropriate approach is obtaining the same medical history and evaluation as for patients with general chest pain and determining the choice of tests based on symptoms [3, 33, 34]. In addition, differentiation of emergency conditions and severe cardiac diseases should be prioritized, and referral to the appropriate specialty is recommended based on the urgency and severity of symptoms and test results [3, 35]. At present, no compelling evidence supports the routine use of blood tests or imaging studies for patients with PASC. However, serum troponin and electrocardiogram testing may be considered for assessment of myocardial injury. In cases of abnormal findings, echocardiography and cardiac magnetic resonance imaging (cardiac magnetic resonance imaging [MRI]) should be used to evaluate structural abnormalities, such as myocarditis or pericarditis [34, 36]. In particular, for patients who have developed myocarditis as a complication after SARS-CoV-2 infection, the duration until the normalization of troponin levels is unclear; therefore, a single elevated measurement may not necessarily indicate a new cardiac condition. Echocardiography is useful for identifying abnormalities in the myocardium and pericardium in patients with persistent symptoms; it can be utilized as a follow-up examination 2–3 months later in patients who have had acute myocarditis, pericarditis, or heart failure [3]. A meta-analysis reported that the incidence rate of myocarditis following COVID-19 was 0.21 cases per 1,000 individuals during an average 9.5-month follow-up period, higher than that observed in non-infected individuals (0.09 cases per 1,000) [37]. Meanwhile, chest pain in patients with PASC is not exclusively attributable to cardiovascular factors. Noncardiac causes, including chest wall (costochondritis and myalgia), respiratory (hyperventilation syndrome and pleurisy), and gastrointestinal (esophageal spasm and gastroesophageal

reflux) issues, are also common, underscoring the necessity of considering these possibilities as well [35].

Based on current evidence, despite the absence of a standardized testing protocol for patients with PASC presenting with chest pain, a stepwise approach to rule out cardiovascular, respiratory, musculoskeletal, and gastrointestinal disorders seems reasonable, while fundamentally following clinical guidelines for evaluation and treatment of general chest pain [6, 10].

3) What is the evaluation method for patients with PASC who complain of cough?

Recommendation

- Patients with PASC who present with a cough should undergo a chest X-ray and, if indicated, a chest CT scan to evaluate for the presence of pulmonary fibrosis or bronchial damage (G, I).
- In accordance with the findings of experts, the performance of pulmonary function tests and fractional exhaled nitric oxide testing may be indicated (G, I).

The prevalence of persistent cough after COVID-19 was 18% (95% CI, 12–24%; $I^2 = 93\%$) among patients hospitalized with COVID-19 when followed for 6 weeks to 6 months. However, the prevalence varied depending on the characteristics of the study patients, treatment, and follow-up period. Although the cause of persistent coughing after COVID-19 remains unclear, it may be associated with chronic fatigue, dyspnea, chronic pain, and the SARS-CoV-2 invading sensory nerves that mediate coughing, leading to hypersensitivity of the cough reflex. Furthermore, the presence of fibrosis of the lung parenchyma or damage to the bronchi due to mechanical ventilation increases the sensitivity of the cough reflex. Consequently, its evaluation is of significant importance, and its confirmation can be achieved through chest CT [38].

According to guidelines for the management of chronic cough by the Korean Academy of Asthma, Allergy and Clinical Immunology, a detailed medical history, physical examination, and plain chest X-ray are essential for evaluation of chronic cough. Pulmonary function tests may be performed to rule out chronic obstructive pulmonary disease. To rule out potential causes not been identified on chest X-ray, additional tests such as chest CT and bronchoscopy may be performed.

Measurement of fractional exhaled nitric oxide (FeNO) is recommended for the diagnosis of cough-variant asthma and eosinophilic bronchitis [39]. However, 2019 European Respiratory Society guidelines advise against performing chest CT when chest X-rays show no specific findings, as bronchiectasis or pulmonary nodules not visible on X-ray are unlikely to be the cause of cough. Additionally, the recommendation for FeNO measurement was put on hold [40]. Song et al. recently conducted a prospective and retrospective study of a patient cohort who reported persistent cough following COVID-19 and compared clinical characteristics of this group with those of patients experiencing chronic cough unrelated to COVID-19. While no differences were found in cough severity, plain chest X-ray findings, or pulmonary function tests, elevated FeNO levels were more frequently observed in the post-COVID-19 persistent cough group, suggesting a potential association with asthma or eosinophilic bronchitis [41].

While a persistent cough after COVID-19 is a common symptom, various guidelines do not explicitly specify evaluation methods or provide supporting evidence. Therefore, evaluation is recommended based on the clinical presentation of chronic cough, with the possibility of new evidence being added in the future as research results emerge.

4) What is the evaluation method for patients with PASC who complain of fatigue?

Recommendation

- No singular, specific evaluation test can assess fatigue symptoms in patients with PASC (G, III).
- Fatigue assessment should be conducted through the differentiation of physical and mental domains using a multidisciplinary approach, including employment of self-reports and standardized fatigue scales (e.g., Fatigue Severity Scale (FSS), Chalder Fatigue Scale (CFS), DSQ-SF, and Visual Analogue Scale (VAS)) (A, IIa).
- A comprehensive medical history, encompassing social and psychological factors, medications, sleep disorders, underlying medical conditions, and COVID-19 sequelae, together with a physical examination, is essential (G, IIa).
- If indicated, blood tests, electromyography, imaging studies, and functional tests (6-min walk test, tilt test, etc.) should be performed to rule out organic causes (G, IIa).
- This comprehensive approach enables the elimination

of organic causes and facilitates the development of customized rehabilitation and management strategies for each patient (G, IIa).

Identification of fatigue symptoms in patients with PASC can be facilitated through self-reporting or use of standardized fatigue assessment tools. Several criteria have been developed to describe fatigue syndrome [42–44]. Recent RCTs have employed the FSS, CFS, DePaul Symptom Questionnaire-Short-Form (DSQ-SF), and VAS [45–48]. Generally, FSS and CFS can be used for evaluation [49]. CFS is a self-report questionnaire designed to assess the severity and impact of an individual's fatigue and is often used to measure fatigue in clinical and research settings. CFS consists of 11 items describing various symptoms associated with physical and mental fatigue (Table 4). Each item is scored using a Likert scale (0–3 points), with zero indicating “less than usual” and three indicating “much more than usual.” A total score is calculated by summing the scores for each item, with a higher total score indicating a higher level of fatigue. For patients complaining of fatigue, FSS can be used to assess the level of fatigue (Table 5). FSS consists of a total of nine items to assess the level of fatigue over the past week on a scale of 1–7 points. The sum of the scores for each item is divided by nine to determine the final score. A higher FSS score indicates a higher level of fatigue. Additionally, DSQ-SF can be used to assess the frequency and severity of key symptoms over the past 6 months for each of the seven items on a scale of 0–4 (Table 6). Subjective intensity of symptoms such as pain, fatigue, anxiety, and depression can be quantified using the widely employed VAS (Table 7).

Recent international guidelines and research highlight different assessment and management strategies. According to the WHO guidelines, the presence of PESE must be confirmed, and symptom-titrated physical activity should be implemented [50]. The NICE (2024) guidelines specified fatigue as the most common symptom of PASC and presented integrated assessment and management strategies, including patient education, self-management support, and multidisciplinary rehabilitation coordination [3]. The Swiss guidelines recommended using the Fatigue Scale for Motor and Cognitive Functions and included assessments for differential diagnoses such as iron deficiency, sleep apnea, and medications [35]. The New Zealand guidelines emphasized the need for a comprehensive assessment of

Table 4. Chalder fatigue scale

Question	Domain (conceptual)
1. Do you have problems with tiredness?	Physical/General
2. Do you need to rest more?	Physical/General
3. Do you feel sleepy or drowsy?	Physical/General
4. Do you have problems starting things?	Mental
5. Do you lack energy?	Physical/General
6. Do you have less strength in your muscles?	Physical
7. Do you feel weak?	Physical
8. Do you have difficulty concentrating?	Mental
9. Do you make slips of the tongue when speaking?	Mental
10. Do you find it more difficult to find the correct word?	Mental
11. How is your memory?	Mental
Feature	Detail
Scoring scale	Likert scale of 0 to 3 points for each item
Scale Anchors	0 = "less than usual" 3 = "much more than usual"
Total Score	Calculated by summing the scores of all 11 items
Interpretation	A higher total score indicates a higher level of fatigue

Table 5. Fatigue severity scale

Question	Never		Not really			Yes		
1 When you are tired, you lose motivation.	1	2	3	4	5	6	7	
2 Exercise makes you feel tired.	1	2	3	4	5	6	7	
3 You tire easily.	1	2	3	4	5	6	7	
4 Physical activity declines due to fatigue.	1	2	3	4	5	6	7	
5 Fatigue often causes problems.	1	2	3	4	5	6	7	
6 Fatigue makes it difficult to engage in sustained physical activity.	1	2	3	4	5	6	7	
7 Fatigue prevents you from fulfilling your duties or responsibilities.	1	2	3	4	5	6	7	
8 If you were to choose the three most difficult problems you are facing, fatigue would be one of them.	1	2	3	4	5	6	7	
9 Fatigue interferes with work, family, and social activities.	1	2	3	4	5	6	7	

Table 6. DePaul symptom questionnaire-short form (DSQ-SF)

Domain	Symptom	Frequency (0-4)	Severity (0-4)
Fatigue and recovery	Fatigue/extreme tiredness		
	Unrefreshing sleep		
	Post-exertional malaise		
Sleep disorder	Difficulty falling asleep		
	Problems staying asleep		
Pain	Muscle pain		
	Joint pain		
	Headaches		
Cognitive deficits	Memory problems		
	Difficulty concentrating		
Autonomic nervous system symptoms	Dizziness/faintness		
	Heart palpitations		
Immune and gastrointestinal systems	Sore throat		
	Tender lymph nodes		
	Nausea, bloating, or stomach pain		
Hypersensitivity and other conditions	Sensitivity to light/noise		
	Temperature intolerance		

fatigue encompassing quality of life, social functioning, and the potential for return to work [51].

For patients with PASC presenting with fatigue, the first step is to investigate potential sociopsychological

or emotional factors, medications, sleep disorders, or toxin exposure that could contribute to their fatigue.

In addition, a detailed medical history and physical examination are essential to determine the presence of any underlying conditions potentially associated with

Table 7. Visual analogue scale (VAS)

Category	Description	Examples
Purpose of evaluation	Quantifying the intensity of subjective symptoms for objective comparison and monitoring of progression	Pain, fatigue, anxiety, sleep quality, etc.
Scale type	Extreme conditions are marked at both ends of a 10-cm or 100-mm straight line	"No pain" "The most severe pain imaginable"
Assessment method	Indicating the severity of the current symptoms on the straight line	e.g., Marking at the 6.8 cm point
Score conversion	Scoring by measuring the distance (cm or mm) from the left end (0 points) to the marked position	e.g., 6.8 cm → 68/100 points
Score interpretation (e.g., fatigue)	0-3: mild/4-6: moderate/7-10: severe	VAS 8 → Severe fatigue

current fatigue, the existence of sequelae from severe COVID-19, or other organic causes [36]. An assessment of inpatient treatment during COVID-19 illness (including length of hospitalization and ICU admission status) is required. In addition, a review of medication history, such as use of anesthetics or steroids, should be undertaken. Furthermore, past medical history regarding previous neurological and musculoskeletal disorders should be evaluated. The range of motion and presence of contractures in all major joints should also be assessed. For neurological assessment, evaluation of muscle status (e.g., light touch, pinprick vibration, proprioception, and temperature sensation tests) and gait assessment (tandem gait) may be performed. In addition to taking a medical history and performing a physical examination, muscle enzyme levels such as creatine kinase, lactate dehydrogenase, and myoglobin are evaluated for differential diagnosis. Additionally, tests may include a complete blood count (CBC) with differential counts, electrolyte panel (sodium, potassium, chloride, bicarbonate, calcium, phosphate, etc.), liver function tests, and renal function tests (blood urea nitrogen and creatinine). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid function tests, blood cortisol, rheumatoid factor, and anti-nuclear antibody levels may also be evaluated. In addition to blood tests, electromyography may be performed. If indicated, a CT or MRI scan may be used to evaluate the presence of anatomical abnormalities in the musculoskeletal system. Functional assessments, such as the 6-min walk test or the sit-to-stand test, may also be conducted [3].

5) What is the evaluation method for patients with PASC who complain of joint and muscle pain?

Recommendation

- Patients who have experienced joint pain or muscle pain for more than 3 months following SARS-

CoV-2 infection may undergo further evaluation; this evaluation may be based on their medical history and physical examination. Additionally, if symptoms persist, a referral to a specialist department may be considered (G, IIb).

A Korean study examining patients six and 12 months after COVID-19 diagnosis found that joint pain was reported by 11% of patients at 6 months and 7% at 12 months, while muscle pain was reported by 6% at 6 months and 2% at 12 months [11]. These rates were similar to those found in other international studies. Joint pain was found in 10–48% at 4–12 weeks and 9% at 3–6 months (95% confidence interval, 5.7–15 months), while muscle pain was found in 1–32% at 4–12 weeks and 11% at 3–6 months (95% confidence interval, 6.2–19.8 months) [52, 53]. Furthermore, a meta-analysis of patients who recovered from severe COVID-19 revealed that muscle pain was experienced by 5.65–18.15% of patients and joint pain by 4.6–12.1% of patients within the first year [54].

An observational study of 20 patients with PASC exhibiting neuromuscular symptoms found no abnormalities in nerve conduction studies. However, electromyography revealed abnormalities in 55% (11 out of 20) of the patients [55]. However, due to the small size of the observational study and because only a subset showed abnormal findings, evidence is insufficient to recommend or restrict this test for all patients with PASC complaining of muscle pain symptoms.

Despite the absence of definitive research evidence to substantiate the specific evaluations to be administered to patients with muscle or joint pain, guidelines from other nations have enumerated tests and referrals that may be considered for cases of persistent joint or muscle pain [3, 35, 51]. Some guidelines cite blood tests such

as CBC, liver and kidney function, CRP, serum ferritin, and thyroid function as examples of tests that may be performed if indicated [3]; however, these guidelines do not advocate for a comprehensive panel to be performed routinely. Other guidelines prioritize medical history taking and physical examination, with general tests including CBC, ESR, CRP, and creatine kinase for significant muscle pain and weakness. Testing for thyroid-stimulating hormone may be considered for suspected conditions. Specialist consultation (rheumatology, neurology for muscle weakness) is recommended for symptoms persisting over 3 months [35].

6) What is the evaluation method for patients with PASC who complain of headaches?

Recommendation

- Evaluation of headaches associated with PASC should encompass a medical history, neurological examination, and vital signs (G, I).
- In the absence of neurological red flag signs, management of this condition should align with the standard protocol for primary headache disorders (G, I).
- In instances where a differential diagnosis of secondary headaches is required, implementing of brain imaging studies and referring patients to a neurologist for specialized evaluation and treatment is advised (G, I).

Headache is one of the common symptoms in COVID-19 patients (reported in 14%–60% of cases, varying by study) and can persist for weeks, even after the acute phase of the disease has subsided [56]. A meta-analysis study has reported that 15% (95% CI, 4.5–25.8%) of individuals still experience headaches 3 months after COVID-19 [57]. PASC-related headaches can present either worsening of preexisting headaches or the onset of new headaches. A common characteristic is the near-daily persistence of headaches that occur either at the time of COVID-19 diagnosis or shortly thereafter. This may be attributed to the immune and inflammatory responses activated during infection, which can trigger headache symptoms or exacerbate or prolong existing migraines [58].

PASC-related headaches may conceivably not be attributable to persistent infection with the SARS-CoV-2 virus itself. Rather, these headaches may be the result of neuro-immunological changes that

persist subsequent to viral infection [1]. Reports have documented the occurrence of new daily persistent headaches that persist for a duration exceeding 3 months following previous EBV infections. Additionally, accounts are available regarding new daily persistent headaches that manifested subsequent to the 1890 Russian flu pandemic infection [59, 60]. Further investigation is warranted regarding the similarities between new daily persistent headaches following infection and headaches associated with PASC.

The primary concern when experiencing a headache is to rule out the possibility of a secondary headache caused by an underlying condition. A thorough medical history should first be obtained to carefully assess the onset, characteristics, duration, aggravating factors, and accompanying symptoms of the headache. A neurological examination should then be conducted to evaluate any potential localized neurological abnormalities. Particularly, headaches that occur suddenly and reach peak intensity within 1 min (thunderclap headaches); those accompanied by systemic symptoms such as fever, vomiting, or weight loss; new headaches in cancer patients or immunosuppressed patients; cases with associated focal neurological abnormalities (motor or sensory deficits, visual field defects, speech impairment, etc.); cases where papilledema is observed; headaches that progressively worsen over time; headaches that worsen upon standing or are triggered by the Valsalva maneuver; and new headaches occurring after head trauma or while taking anticoagulants represent “red flag signs” suggesting the possibility of secondary headaches. These findings necessitate an evaluation for organic causes. Imaging studies such as brain MRI or brain CT should be considered, and referral to a neurologist is required.

In the absence of such red flag signs and neurological abnormalities and if organic causes are ruled out, treatment is administered as for primary headaches such as migraines or tension-type headaches [1, 35, 61].

7) What is the evaluation method for patients with PASC who complain of cognitive impairment or brain fog (concentration or attention deficit)?

Recommendation

- In patients exhibiting cognitive impairment or brain fog (concentration or attention deficit), potential

causes such as psychiatric disorders, sleep disorders, medication-associated adverse events, and endocrine, autoimmune, or infectious diseases should be evaluated through detailed medical history taking, neurological examination, and neuropsychological testing (G, I).

- In cases where local neurological abnormalities or brain lesions are suspected, imaging studies, including brain magnetic resonance imaging, should be performed (G, I).
- For cognitive impairment lasting over 3 months or causing functional disability in daily life, work, or studies, cognitive screening tests such as Montreal Cognitive Assessment and Symbol Digit Modalities Test should be administered. If indicated, a multifaceted assessment, including neuropsychological testing, sleep evaluation, and quality of life assessment (EQ-5D-5L, Barthel Index, etc.), should be considered.
- For persistent cognitive impairment or attention deficits, referral to a specialist such as a cognitive rehabilitation specialist or psychiatrist should be considered (G, IIa).

Reports of cognitive impairment or brain fog following SARS-CoV-2 infection are relatively common. In a meta-analysis conducted in patients more than 3 months after the onset of COVID-19, the prevalence of brain fog was 32% (95% CI, 10.3–54.0) and that of memory impairment was 28% (95% CI, 21.5–35.4) [60]. A Korean study also reported concentration deficits in 22%, memory impairment in 20%, and cognitive decline in 21% at 6- and 12-month follow-ups [10, 62]. Patients frequently report a range of symptoms, including difficulties concentrating during work or daily activities, slowed processing speed, executive dysfunction, impaired memory or recall, and the loss of train of thought. These symptoms are frequently characterized by the term "brain fog" [50, 51, 63]. Such cognitive symptoms require a detailed medical history taking, neurological examination, and neuropsychological testing. Differential diagnosis may

be required for secondary factors such as endocrine disorders, autoimmune diseases, infectious diseases, psychiatric disorders (depression, anxiety, PTSD, etc.), sleep disorders, and medication-associated adverse events [3]. **Table 8** lists representative medications that may affect cognitive function [64]. In younger patients, sleep disorders, mood disorders, and fatigue have been identified as significant contributing factors. In elderly patients with persistent delirium, the possibility of underlying dementia should be considered [8]. A determination should be made concerning whether patients are taking any medications that could cause cognitive decline. If an underlying disease is suspected, referrals to relevant specialists such as neurologists, psychiatrists, rheumatologists, or endocrinologists should be considered. In cases of cognitive impairment with a duration exceeding 3 months or leading to impairment in occupational, academic, or daily functioning, administration of standardized cognitive screening tests, such as the Montreal Cognitive Assessment and the Symbol Digit Modalities Test, is recommended. If indicated, a multifaceted assessment is recommended, including neuropsychological testing, sleep evaluation, and quality of life assessment (EQ-5D-5L, Barthel Index, etc.) [35]. In cases where attention deficits are the primary concern, specialized tests such as the Digit Span, Digit Vigilance Test, and Cancellation Test can be utilized.

In instances where focal neurological deficits are identified during neurological examinations or when brain lesions are suspected, imaging studies such as MRI are recommended [1, 64]. If cognitive impairment is evident or if a differential diagnosis is required, referral to specialized departments such as neurology or psychiatry should be considered [3, 11, 62, 64–66]. In a 12-month follow-up study of survivors among severe COVID-19 patients, approximately 30% exhibited objective cognitive impairment, with particularly pronounced declines in executive function, processing speed, and recognition memory [67]. Female sex and PTSD were

Table 8. Medications that may affect cognitive function [64]

Classification	Examples
Anticholinergics	
First-generation antihistamines	Diphenhydramine, hydroxyzine, and meclizine
Antispasmodic	Scopolamine
Central nervous system agents	
Antidepressants	Amitriptyline, nortriptyline, and paroxetine
Antipsychotics	Risperidone, quetiapine, olanzapine, and ziprasidone
Benzodiazepines and sleep-inducing agents	Alprazolam, diazepam, lorazepam, temazepam, eszopiclone, zaleplon, and zolpidem
Muscle relaxants	Varisoprodol and cyclovenzaprine

identified as risk factors, while high cognitive reserve was identified as a protective factor. Moreover, positron emission tomography-CT (PET-CT) studies show that hypometabolism in specific brain regions following SARS-CoV-2 infection is associated with reduced olfactory function, impaired memory and cognitive abilities, and insomnia [68]. Therefore, a multifaceted approach integrating screening tests, neurocognitive assessments, and the evaluation of comorbid factors is recommended for assessment of cognitive impairment in patients with PTSD. If indicated, imaging studies such as MRI or PET-CT and referral to specialists should be considered for differential diagnosis and rehabilitation approaches.

8) What is the evaluation method for patients with PASC who complain of anxiety or depression?

Recommendation

- In cases of severe psychiatric symptoms or risk of self-harm or suicide, immediate referral for psychiatric evaluation and treatment is recommended (G, I).
- A referral to a psychiatrist is recommended to rule out the presence of psychiatric disorders that could explain depression or anxiety (G, I).
- During the assessment process, a wide range of potential mental health conditions, including depression, anxiety, post-traumatic stress disorder, and adjustment disorder should be considered. A comprehensive, multifaceted evaluation is recommended, including an analysis of their psychiatric history, family history, social support networks, and suicide risk (G, I).
- The Hospital Anxiety and Depression Scale and the Patient Health Questionnaire-9 can be used as screening tools; however, clinical evaluation is recommended in conjunction with these tools for diagnosis (G, I).
- Early identification of high-risk groups can be facilitated by evaluating major risk factors, such as female sex, prior psychiatric history, acute-phase inflammation, uncertain recovery, and cognitive impairment (G, IIa).

International guidelines recommend a prompt referral of COVID-19 patients with persistent symptoms or suspected PASC who exhibit severe psychiatric symptoms or risk of self-harm or suicide for psychological evaluation [3]. Referrals to psychiatric services are also recommended to explore various possibilities such as depression, anxiety,

PTSD, and adjustment disorders, and to distinguish between cognitive impairment and psychiatric issues [35].

For this purpose, the Hospital Anxiety and Depression Scale, Beck Depression Inventory fast screen, Geriatric Depression Scale, Patient Health Questionnaire (PHQ-2/9 or PHQ-8), Generalized Anxiety Disorder-7, and PTSD Checklist-5 may be used [63]. While screening tests can be utilized, they are not adequate for diagnosis alone. A comprehensive, multifaceted clinical approach is imperative, encompassing the evaluation of psychiatric history, family history, social support networks, and suicide risk [2]. Several significant risk factors have been identified, including female sex, a prior psychiatric history, acute-phase inflammation, and uncertainty regarding recovery. Of particular note is the emphasis on the potential for concurrent cognitive decline [51].

A systematic literature review and meta-analysis reported that among the long-term neurocognitive effects, COVID-19-associated psychiatric symptoms included PTSD at 31%, depression at 20%, and suicidal tendencies at 2% [64]. Furthermore, the hospitalized group exhibited a higher prevalence of anxiety (OR, 3.09), depression, muscle pain, and hair loss than the non-hospitalized group [62]. Individuals with prior experience of ICU admission exhibited an elevated long-term risk of functional decline, PTSD, and depression [69, 70]. A neuropsychological outpatient study revealed that the disorders with the highest prevalence were somatic preoccupation and depression [66]. Furthermore, the presence of preexisting neuropsychiatric or substance use disorders has been identified as a factor that can increase the risk of COVID-19 progression and long-term complications [65, 71]. Finally, socioeconomic factors affecting patients (poverty, discrimination, and social isolation) and their mental health management should be considered. Social connectedness, support networks, and community-based interventions are significant protective factors for the mental health recovery and well-being of patients with PASC [61].

9) What is the evaluation method for patients with PASC who complain of sleep disorders?

Recommendation

- A review of sleep patterns and assessment of factors interfering with sleep (habits, substances, and environment) as well as underlying conditions such as

sleep apnea, restless legs syndrome, pain, and anxiety is recommended (G, I).

- For differential diagnosis and evaluation of complex symptoms, a referral to a sleep medicine specialist or psychiatrist should be considered (G, IIa).
- A multifaceted approach may be considered during diagnosis, utilizing screening tools (e.g., the Insomnia Severity Index), sleep history and sleep diaries, and objective assessment tools such as actigraphy if indicated (G, IIb).

A meta-analysis has indicated that approximately 34–46% of patients with COVID-19 experience sleep disorders, which are strongly associated with depression (45%) and anxiety disorders (57%) [72]. Specifically, 56% reported poor sleep quality, 38% reported insomnia, and 14% reported excessive daytime sleepiness [73]. Disruption of the sleep-wake cycle and circadian rhythm has been associated with impaired cognitive functions, including attention, concentration, and memory, which is a salient concern for patients with PASC [74].

International guidelines recommend confirming the following at diagnosis: ① sleep history before and after COVID-19; ② comorbidities such as nightmares, sleep apnea, restless legs syndrome, or pain; ③ lifestyle habits, including exercise, alcohol consumption, medication use, and caffeine intake; and ④ use of sleep aids or behavioral strategies [75]. An assessment of insomnia severity using the Insomnia Sleep Index is recommended, along with evaluation of the level of fatigue and any neurological or psychiatric comorbidities. If indicated, objective testing via actigraphy or polysomnography is recommended [50]. Certain medications (antidepressants, beta-blockers, diuretics, etc.) and ICU treatment history (e.g., mechanical ventilation) have also been reported as risk factors for sleep disorders [76]. Brain imaging studies have also identified the association of metabolic decline in specific brain regions among patients with COVID-19 with symptoms such as insomnia, anosmia, and memory impairment [68]. Therefore, a multifaceted approach encompassing clinical symptoms, screening tools, medical history, lifestyle habits, and physical and mental health factors is required for the diagnosis of sleep disorders in patients with PASC.

10) What is the evaluation method for patients with PASC who complain of swallowing disorders (dysphagia)?

Recommendation

- For the diagnosis of PASC-related swallowing disorders, a video fluoroscopic swallowing study or fiberoptic endoscopic examination of swallowing may be performed, and referral to a specialist in swallowing disorders is recommended (G, I).

Approximately 30% of patients hospitalized with COVID-19 may require additional medical interventions for swallowing disorders [77]. Risk factors included advanced age, chronic neurological or respiratory disorders, endotracheal intubation, mechanical ventilation, prolonged bed rest, persistent cognitive impairment, and underlying dysphagia. In the aftermath of the onset of COVID-19, the occurrence of swallowing disorders is associated with various factors, including tissue damage caused by medical device insertion, direct tissue damage or secondary neuropathy due to SARS-CoV-2 infection, and weakness and muscle loss in muscles related to swallowing [78].

Since swallowing disorders significantly increase the risk of aspiration pneumonia, early diagnosis is essential. A preliminary screening test is recommended prior to undergoing a definitive diagnostic test for swallowing disorders. According to clinical guidelines developed by the Korean Academy of Rehabilitation Medicine and the Korean Dysphagia Society, the 3-ounce water swallowing test may be used for initial screening. If there is a high risk of aspiration during the water swallowing test, the standard screening tests, such as the Burke dysphagia screening test, Gugging Swallowing Screening Test, Standardized Swallowing Assessment, Toronto Bedside Swallowing Screening Test, or Clinical Functional Scale for Dysphagia, may be performed [79]. The diagnostic tests include videofluoroscopic swallowing study or fiberoptic endoscopic examination of swallowing. Both tests can be performed complementarily depending on the condition of patients.

11) What is the evaluation method for patients with PASC who complain of olfactory or gustatory disorders (anosmia, hyposmia, or dysgeusia)?

Recommendation

- If patients with PASC present with olfactory or gustatory disorders, other organic causes may be ruled out first; no primary assessment tool is recommended for evaluating olfactory or gustatory disorders (G, IIb).

When patients continue to report gustatory or olfactory disturbances after a COVID-19 diagnosis, underlying organic causes may be ruled out first. In patients presenting with gustatory symptoms, it is essential to prioritize evaluation for potential oral or dental disease. Given the established correlation between gustatory disorders and olfactory dysfunction, assessing the presence of olfactory disorders is also vital. When patients present with olfactory disorders, preliminary evaluation should prioritize assessment of allergic rhinitis and chronic sinusitis. Assessment for traumatic brain injury or neurodegenerative disorders (Parkinson's disease, Alzheimer's disease, and mild cognitive impairment) may also be indicated. Another essential check is whether patients are taking medications that may cause olfactory disorders (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, etc.) [80]. For persistent symptoms or delayed recovery, evaluation by an otolaryngologist or other specialist is recommended.

Research regarding evaluation of olfactory or gustatory disorders in COVID-19 patients is scarce. In a systematic review of qualitative olfactory function assessments, Annelin et al. analyzed 72 studies, finding that only four objective olfactory assessment tools, including the Chemosensory Perception Test, Yale Jiffy Smell Identification Test, SCENTinel 1.1, and Sniffin' Stick test, were being used. The most frequently used subjective assessment tools included NHANES, QoD, and GCCR [81]. While objective evaluation is advantageous in providing consistent data, it cannot assess phantosmia (the perception of odors that do not exist), which is a limitation. The available data do not permit a definitive conclusion regarding the relative merits of any of the assessment tools under consideration.

The mechanism of olfactory or gustatory disorders involves SARS-CoV-2 virus infection of olfactory epithelial

supporting cells that express angiotensin-converting enzyme-2, resulting in damaged olfactory nerve cells. While olfactory or gustatory disorders typically recover gradually within weeks to months, a parametric treatment model study by Benjamin et al. based on a systematic literature review demonstrated that approximately 5% of patients experienced persistent functional impairment, with females in particular showing a lower likelihood of recovery in both olfactory and gustatory functions [82]. Long-term follow-up observation is warranted for olfactory or gustatory disorders.

12) What is the evaluation method for patients with PASC who complain of PEM/PESE?

Recommendation

- If patients with PASC present with motor abnormalities, assessment of such abnormality may be conducted through the utilization of questionnaires, with cardiopulmonary exercise testing serving as the confirmatory test (G, IIb).

PEM, or PESE, denotes exacerbation of preexisting symptoms or emergence of new symptoms following physical or cognitive activity. PEM or PESE is a set of distinct symptoms that do not correspond to the typical fatigue experienced by healthy individuals after overexertion. Symptoms may be exacerbated during exercise, and the timing of onset may vary from hours to months after SARS-CoV-2 infection. PEM or PESE may ensue in response to activities that individuals were capable of performing previously (e.g., showering, cooking, conversation, or reading). These activities can potentially trigger PEM or PESE in previously healthy individuals [83]. The pathophysiology of PEM or PESE remains largely unclear; however, PEM arises from various bioenergetic dysfunctions (e.g., abnormal endothelial responses; alterations in brain function and cognitive impairment; orthostatic intolerance; changes in methylation and acetylation affecting gene expression and protein function; alterations in the gut microbiota, etc.) [84].

A 10-item questionnaire can be utilized for the screening for PEM or PESE (Fig. 2) [85]. When PEM or PESE is suspected based on the results of the questionnaire, a comprehensive evaluation can be performed using the DePaul Post-Exertional Malaise Questionnaire [86]; this questionnaire consists of 53 items (items 13–66)

Symptoms	Frequency:	Severity:
	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	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

Figure 2. PEM/PESE screening questionnaire.

PEM, post-exercise malaise; PESE, post-exertional symptom exacerbation.

that assess the frequency and intensity of symptoms on a Likert scale ranging from 0 to 4. This allows for identification of the triggers, symptoms, associated outcomes, and duration of PEM or PESE.

When patients experience fatigue, a series of tests may be utilized to assess their level of physical activity and muscle strength. Anaerobic capacity can be assessed using the 30-s sit-to-stand test, aerobic capacity using CPET, and muscle strength using the handgrip test.

The use of graded exercise therapy, which involves a gradual increase in physical activity under physician supervision, may actually lead to functional decline in patients with PEM or PESE [87, 88]. Therefore, two consecutive days of CPET testing are required to confirm that patients with PEM or PESE exhibit different responses compared with healthy individuals.

In summary, patients with PEM or PESE show reduced myocardial workload and an inability to increase oxygen consumption, heart rate, or systolic blood pressure during the second test compared with the first.

13) What is the evaluation method for patients with PASC who complain of POTS?

Recommendation

- If patients with PASC present with tachycardia upon posture change, the NASA Lean Test or head-up tilt test may be considered (G, IIb).

POTS is a chronic condition that manifests when an individual transitions from a seated or recumbent position to an upright posture. It is characterized by an increase in heart rate of 30 beats per minute or more, or a heart

rate of 120 beats per minute or more, when transitioning from a supine to a standing position, in the absence of evidence of orthostatic hypotension [89].

This phenomenon may indicate concurrent overactivity of the sympathetic nervous system and diminished function of the vagus nerve (parasympathetic nervous system) in the supine position. Autonomic dysfunction caused by SARS-CoV-2 viral infection is reported to be multifactorial in nature, involving a range of factors including immune dysregulation, hormonal disturbances, viral penetration of the brain, elevated cytokine levels, direct tissue damage, vasculitis, microthrombosis, and persistent infection [90]. Palpitations and chest pain are the most commonly observed symptoms in POTS. Moreover, cases of exercise intolerance, fatigue, and vasovagal syncope have been documented.

In instances where POTS symptoms are suspected, the NASA Lean Test or head-up tilt test can be utilized to identify alterations in heart rate and blood pressure while in a supine position and subsequent to standing [91]. During examination, acrocyanosis (purple discoloration of the extremities) is observed in approximately 50% of patients. If POTS is not confirmed by these tests, the Valsalva maneuver test and deep breathing test may be considered.

Inflammation or autoimmune-related markers may also be measured [92]. G-protein-coupled receptors (alpha adrenoreceptor, beta-adrenoreceptor, angiotensin II, nociceptin, and muscarinic), ganglionic neuronal nicotinic acetylcholine receptor, circulating anti-nuclear, antithyroid, anti-NMDA-type glutamate receptor, anti-opioid-like-1 receptor, anti-cardiac protein, anti-phospholipid, and Sjögren's antibody may be assessed. Routine tests may include a CBC, albumin, renal function, electrolytes, NT-pro-BNP, TSH, and morning cortisol. Holter monitoring is also helpful for diagnosing POTS. To rule out other conditions, 24-h ambulatory blood pressure monitoring, chest X-ray, echocardiogram, chest CT, cardiac MRI, and exercise stress testing may also be considered [93]. In cases of severe impairment, the 6-min walk test may be employed to assess peripheral oxygen desaturation and flat breathing.

5. TREATMENT

(1) What are the treatment modalities for symptoms of PASC?

1) How is dyspnea treated in patients with PASC?

Recommendation

- Current evidence does not support recommending specific pharmacologic therapies for the treatment of dyspnea in patients with PASC (A, I).
- Respiratory rehabilitation is recommended for patients with PASC who have persistent respiratory symptoms or functional impairment, to improve respiratory symptoms and overall functional capacity (A, I).

While guidelines from various countries do not specify particular treatments for dyspnea in patients with PASC, studies indicate that respiratory rehabilitation can be beneficial in the absence of an underlying disease causing dyspnea (see the question regarding rehabilitation). In cases of persistent dyspnea, following an evaluation of the underlying cause, treatment is recommended for any newly identified condition.

A retrospective observational study was conducted in Spain, surveying 76 patients who were hospitalized with COVID-19 via telephone regarding their symptoms 1 year later. The group that received steroids during acute COVID-19 treatment demonstrated superior recovery in terms of pain, mental health, and general health than the group that did not receive steroids. However, no difference was observed in dyspnea or cough [94]. In a prospective, randomized observational study conducted in Türkiye, 30 patients with confirmed pulmonary fibrosis who had experienced dyspnea, cough, and other symptoms for 12 weeks or more following a diagnosis of severe acute COVID-19 were treated with either nintedanib or pirfenidone for 12 weeks. The study compared lung function, 6-min walk test results, and oxygen saturation levels between the two treatment groups. Both groups exhibited enhanced imaging results and augmented lung function. Notably, nintedanib demonstrated the ability to enhance exercise capacity and oxygen saturation, while concomitantly eliciting a higher incidence of drug-related adverse events than pirfenidone [95]. In a prospective observational study conducted in the UK, among 49 patients with PASC following mild acute COVID-19, 26 received antihistamine therapy (H1 receptor

blockade: loratadine 10 mg or fexofenadine; H2 receptor blockade: famotidine or nizatidine), while 23 did not receive antihistamine therapy. Symptom questionnaires were administered between weeks 4 and 16 of treatment initiation, indicating a marked improvement in symptoms in the antihistamine therapy group. While blood tests of patients with PASC revealed reduced CD4+ and CD8+ cell counts, their responses to antihistamines could not be predicted [96].

2) How is a cough treated in patients with PASC?

Recommendation

- Insufficient evidence exists to recommend specific pharmacologic therapy for cough symptoms in patients with PASC. According to Korean chronic cough treatment guidelines, empirical treatment with antihistamines or inhaled corticosteroids may be considered for symptom control. However, evidence supporting this approach is also limited, and its clinical application may be carefully considered (G, IIb).

Insufficient evidence is available to recommend specific pharmacological therapy for cough symptoms in patients with PASC. During the recent Omicron wave in South Korea, a comparison of clinical characteristics was conducted between 120 patients with persistent cough lasting over 3 weeks following SARS-CoV-2 infection and 100 patients with chronic cough unrelated to COVID-19. Despite the presence of comparable overall profiles, a substantial increase in exhaled nitric oxide levels was observed among patients with COVID-19-associated cough symptoms [41].

Furthermore, a new paradigm shift has emerged, interpreting chronic cough as an independent disease caused by hypersensitivity of the cough reflex circuit rather than a symptom resulting from other diseases. In light of these findings, the Korean Academy of Asthma, Allergy and Clinical Immunology developed clinical practice guidelines for chronic cough in 2018 [39]. For treatment of nonspecific chronic cough without treatable characteristics, H1 antihistamines are recommended as the primary empirical therapy. Inhaled corticosteroids may be administered at high doses for a brief period of 2–4 weeks; however, the recommendation is for patients to undergo objective testing to diagnose asthma and eosinophilic bronchitis prior to treatment. Conversely,

empirical use of leukotriene receptor antagonists and proton pump inhibitors was not recommended due to insufficient evidence [39]. Most clinical practice guidelines are derived from a limited number of studies. Given the characteristics of cough, which is influenced by placebo effects and spontaneous improvement, conducting clinical trials presents significant challenges. Nevertheless, management of cough in patients with PASC may adhere to prevailing clinical guidelines, and further research is warranted in this domain.

3) How is fatigue treated in patients with PASC?

Recommendation

- In the event that neurological or musculoskeletal abnormalities are identified during the evaluation of patients presenting with fatigue, consultation with the relevant specialty is recommended. In the absence of an identifiable organic cause, rehabilitation therapies, including exercise and breathing training, physical therapy, and occupational therapy, may be considered as therapeutic interventions (G, IIb).
- Evidence for treating fatigue in patients with PASC remains limited; however, standardized rehabilitation programs may help improve symptoms. Some adjunctive therapies and medications have demonstrated potential efficacy, but further large-scale studies are warranted (G, IIb).

While a number of approaches, including various medications, alternative medicine, cognitive behavioral therapy (CBT), and exercise, have been considered for treating fatigue symptoms in patients with PASC, a lack of high-level evidence is available to support the effectiveness of these treatments and interventions due to factors such as study design, duration, heterogeneity in fatigue assessment methods, and treatment outcomes [3]. Any neurological abnormalities (such as myopathy or gait instability) identified during the evaluation of patients with PASC who report fatigue symptoms should prompt consultation with a neurologist. In the event that musculoskeletal abnormalities or inflammatory myopathies are identified, consultation with an orthopedic specialist and a rheumatology specialist is limited. In the absence of identified underlying causes related to fatigue, consideration should be given to rehabilitation therapies such as muscle strengthening, stretching, balance training, gait training, aquatic

therapy, yoga, and physical therapy [75]. Furthermore, for patients requiring equipment due to rehabilitation or fatigue, recommendations can be made for helpful devices or for adaptive assistive devices [97]. Persistent symptoms without organic causes may warrant consultation with specialists in psychiatry or in clinical psychology [3].

A multitude of clinical studies have documented the therapeutic and interventional effects regarding fatigue in patients with PASC. Recent RCTs and meta-analyses have confirmed that standardized rehabilitation programs, particularly exercise and breathing training, have the potential to contribute to improvements in functional exercise capacity, fatigue, and quality of life. Pouliopoulou et al. revealed the effectiveness of these rehabilitation interventions in improving physical function and quality of life in patients with PASC through a systematic review and meta-analysis [46]. In a study evaluating a virtual pulmonary rehabilitation program Sarmiento et al. demonstrated improvements in fatigue and cognitive function based on the DSQ-SF, as well as high patient satisfaction and safety [48]. In a randomized, single-blind study, Tan et al. demonstrated that the group consuming hydrogen-rich water for 14 days exhibited significant improvements in Fatigue Severity Scale scores, 6-min walk distance, and sleep quality. However, no effects on dyspnea were observed [98]. Guttuso Jr. et al. posited the potential for enhancing cognitive function and mitigating fatigue in a randomized controlled trial employing lithium aspartate, while acknowledging that conclusions were constrained due to the absence of uniformity in secondary endpoint measures [45]. In addition, Nakamura et al. reported that Donepezil did not demonstrate significant improvement effects on fatigue and psychological symptoms [99]. Korapatti et al. emphasized that while biosound therapy demonstrated encouraging results in reducing anxiety, depression, cognitive function, and fatigue, the evidence supporting these findings was considered low due to the study's limited scope and size [100]. Finally, Seo et al. posited in their scoping review that hyperbaric oxygen therapy, selective serotonin reuptake inhibitors, antifibrotic agents, and antiviral drugs may demonstrate potential efficacy in improving fatigue and cognitive function in patients with PASC. However, they concluded that most evidence was based on small-scale studies, underscoring the necessity for future large-scale RCTs to provide more definitive insights [47].

4) How is joint and muscle pain treated in patients with PASC?

Recommendation

- In patients who develop joint pain or muscle pain persisting beyond three months after COVID-19 onset, management should first follow general pain treatment guidelines, applying them according to the characteristics of the pain and any accompanying symptoms (G, IIa).
- In patients with fibromyalgia-like symptoms characterized by widespread pain, fatigue, and functional impairment that persist beyond three months after COVID-19 onset, transcutaneous electrical nerve stimulation (TENS) may be considered as an adjunctive therapy (A, IIb).

A Korean study indicates that approximately 11.2% and 6.2% of individuals experience joint pain and muscle pain, respectively, around 6 months after the onset of COVID-19 [11]. When symptoms are assessed as unlikely to be caused by other conditions, use of analgesics and a treatment approach for fibromyalgia is recommended as general symptom-relief therapy. Guidelines from other countries also present this as an expert recommendation [35], with analgesics, education, and physical therapy being proposed as first-line treatments.

Additionally, medications such as serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine), low-dose tricyclic antidepressants (amitriptyline), and α_2 -ligands (gabapentin and pregabalin) are suggested as second-line treatments when neuropathic pain or numbness symptoms are present. A pilot RCT conducted in 2024 reported improvements in symptoms, fatigue indicators, and gait indicators in patients with fibromyalgia-like symptoms after using high-dose transcutaneous electrical nerve stimulation for 3–5 h daily over 4 weeks, suggesting its potential for application [101]. However, given the study's limitations, including a small sample size (25 participants) and a short follow-up period, further research is warranted.

5) How are headaches treated in patients with PASC?

Recommendation

- For headaches associated with PASC, symptomatic

treatment may be considered as for primary headaches after excluding organic causes. In cases where migraine symptoms are persistent and result in significant disruption to daily life, preventive migraine treatment may be indicated (G, IIb).

Due to a paucity of research, insufficient evidence is available to support appropriate treatment methods for PASC-associated headaches. For patients with pre-existing primary headaches experiencing exacerbation related to COVID-19, symptomatic and preventive treatments may be considered based on the individual characteristics and type of headache [35, 102, 103]. In instances where patients exhibit symptoms consistent with new daily persistent headaches or chronic headaches arising from systemic infection, and their clinical presentation mirrors that of migraine, consideration may be given to implementing migraine preventive treatment.

For PASC-associated headaches, risk of developing medication overuse headaches is notably elevated due to their persistent daily manifestation. Medication overuse headaches may occur upon using triptans or opioid analgesics for more than 10 days per month or non-opioid analgesics for more than 15 days per month over a 3-month period. Consequently, to mitigate the occurrence of medication overuse headaches, patients must receive comprehensive information about this potential adverse effect and the available preventive measures [102]. During a headache attack, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans can be used as acute treatment options. NSAIDs have raised safety concerns in

COVID-19 patients due to their potential role in instigating overexpression of angiotensin-converting enzyme. However, current evidence suggests that they can be safely used for mild headache attacks [104]. In cases of moderate to severe headache attacks, administration of triptans may be considered. The most commonly utilized medications for the treatment of headaches are as listed in **Table 9**.

When headaches are associated with stress stemming from pandemic-related mood disorders, sleep disorders, family issues, workplace challenges, and socioeconomic difficulties, flunarizine and beta-blockers may exacerbate depressive symptoms. Topiramate may induce cognitive impairment, necessitating caution when PASC symptoms are accompanied by cognitive decline or by memory impairment. In conjunction with pharmacologic interventions, lifestyle modifications must be implemented, including maintenance of a regular routine, regular exercise, and avoidance of prolonged fasting [102]. Especially since sleep problems, commonly experienced after COVID-19 onset, are associated with headaches, addressing sleep issues may help manage headaches [1, 105, 106].

6) How is cognitive impairment or brain fog (concentration or attention deficit) treated in patients with PASC?

Recommendation

- If objective cognitive decline is identified on cognitive screening tests or if symptoms of cognitive impairment or brain fog persist, potential causative

Table 9. Commonly used medications for headache treatment [104]

Medication	Mechanism	Daily dose range	Associated adverse events ^a
Preventive treatment			
Propranolol	Beta blocker	20-160 mg	Fatigue, dizziness, depression, and vivid dreams
Flunarizine	Calcium channel blocker	5-10 mg	Weight gain, drowsiness, dry mouth, dizziness, low blood pressure, depression, and Parkinsonism
Amitriptyline	Tricyclic antidepressant	2.5-50 mg	Weight gain, constipation, weakness, dizziness, drowsiness, fatigue, blurred vision, and dry mouth
Topiramate	Antiepileptic medication	12.5-150 mg	Sensory abnormalities, weight loss, and memory impairment
Acute-phase treatment			
Frovatriptan	Triptan	2.5-5 mg	Triptan sensations (numbness, throbbing, strange sensations, warmth, burning, coldness, and pressure or tightness in the body, including the neck and chest), dizziness, drowsiness, fatigue, weakness, headache, and nausea
Naratriptan	Triptan	1-2 mg	Triptan sensations, dizziness, drowsiness, fatigue, weakness, headache, and nausea
Zolmitriptan	Triptan	2.5-7.5 mg	Triptan sensations, dizziness, drowsiness, fatigue, weakness, headache, and nausea

^aMedication overuse headache: Medication overuse headache occurs upon using triptans or opioid analgesics for 10 or more days per month or non-opioid analgesics for 15 or more days per month, over a 3-month period.

factors should be evaluated. These factors may include medication-associated adverse events, neurological disorders, mood disorders, sleep disorders, or endocrine, autoimmune, or infectious diseases. In the event that any such condition is suspected, the patient should be referred to the relevant specialty department (G, I).

- In patients with impaired concentration, attention deficits, or cognitive dysfunction, referral for specialist evaluation and cognitive rehabilitation by a cognitive rehabilitation specialist or a psychiatrist should be considered (G, IIa).
- Non-pharmacological treatments may include education and self-management training, as well as cognitive training (attention training, metacognitive strategies, etc.); if indicated, these may be combined with multidisciplinary rehabilitation programs (G, IIb).
- Lifestyle modifications (adequate sleep, balanced nutrition, medication reevaluation) and tailored aerobic and cognitive stimulation exercise programs are recommended. For some patients, the use of repetitive transcranial magnetic stimulation as an adjunctive treatment may be considered (G, IIb).
- Low-dose naltrexone and the Biosound Therapy System may be considered only in selected cases or specialized settings, given the paucity of evidence supporting their use (C, IIb).

Currently, insufficient evidence is available to support implementation of particular pharmaceutical interventions or management strategies for cognitive impairment or cerebral fog (concentration or attention deficit) in patients with PASC [1, 63]. Consequently, when cognitive decline is identified, factors that may affect cognitive function, such as sleep disorders, pain, and mood disorders (depression, anxiety, etc.), should be addressed first. Concurrently, other medical etiologies, encompassing neurological, endocrine, autoimmune, and infectious diseases, must be ruled out. In instances where such causes are suspected, patients should be referred to the relevant specialty department. In the event that objective cognitive decline is identified on cognitive screening tests or symptoms persist, referring the patient to a neurologist, psychiatrist, or cognitive rehabilitation specialist for further evaluation and treatment is advisable [63]. In older patients, when delirium or cognitive impairment persist even after recovery from acute COVID-19, the possibility of underlying dementia must be considered [51].

Non-pharmacological therapies encompass a range of approaches, including attention process training, metacognitive strategies, timed structured activities, and techniques for minimizing distractions to enhance attention and improve cognitive function [63]. International guidelines recommend a combination of these interventions through a restorative approach, such as repeated learning, cognitive training, and feedback, and a compensatory approach, such as task simplification, energy management, environmental modifications, and use of assistive devices [50]. Furthermore, regular physical activity and lifestyle modifications (adequate sleep, balanced nutrition, and medication reevaluation) improves cognitive function and sleep quality. In addition, incorporation of multidisciplinary rehabilitation, encompassing customized exercise programs developed by physical therapists or training focused on balance and endurance, should be contemplated [51].

For cognitive impairment with a duration of 3 months or more, intervention is recommended, irrespective of the pathological test results. Intervention emphasis is on training in single-task performance, utilization of reminders, and education in information processing strategies through ergotherapy [35]. A systematic review of studies on patients with mild cognitive impairment revealed that repetitive transcranial magnetic stimulation positively affected performance across multiple cognitive domains, including language, concentration, and memory compared with sham stimulation. This finding suggests the potential for applicability to PASC-associated cognitive impairment [107]. A small-scale study has demonstrated the efficacy of low-dose naltrexone and the biosound therapy system in ameliorating symptoms of fatigue, anxiety, and cognitive impairment. However, the evidence level remains limited due to a paucity of RCTs [47, 100].

Based on the information above, these treatments may be selectively considered as adjunctive or experimental interventions. Furthermore, periodically monitoring changes in symptoms even after the patient has returned to daily life is imperative. Finally, acknowledging that fatigue and mood disorders can function as both causes and outcomes of cognitive impairment, necessitating a comprehensive management approach, is crucial.

7) How is anxiety or depression treated in patients with PASC?

Recommendation

- In cases of severe psychiatric symptoms or risk of self-harm or suicide, immediate referral for psychiatric evaluation and treatment is recommended (G, I).
- Referral to a psychiatrist is recommended to rule out psychiatric disorders that may underlie symptoms of depression or anxiety (G, I).
- For depressive symptoms in patients with PASC, administration of selective serotonin reuptake inhibitors may be considered a therapeutic option (C, IIb).
- Antidepressants are not recommended for adjustment disorders. Anxiety disorders can be treated with self-management, short-term medication, and psychotherapy. If indicated, a psychiatric consultation and a multidisciplinary team approach should be considered (G, IIa).
- Peer support, the utilization of social support networks, and suicide risk assessment employing the risk-urgency-danger approach may also be regarded as useful adjunct strategies (G, IIb).

According to international guidelines, a multifaceted approach is recommended, including CBT, tailored exercise, mindfulness, peer support, and antidepressants when necessary [50]. The emphasis on the efficacy of early intervention is a key tenet of this approach, which advocates for the implementation of counseling and subsequent follow-up sessions, individual or group psychotherapy, medication, and multidisciplinary programs tailored to the severity of symptoms [51]. Antidepressants are not recommended for adjustment disorder treatment. For anxiety and sleep disorders, the emphasis is on self-management, relaxation therapy, short-term medication, psychotherapy, and a multidisciplinary team approach. The assessment of suicide risk should be conducted employing the Risk-Urgency-Danger approach [35]. In cases of severe symptoms or suicide risk, immediate psychiatric referral is facilitated. For mild symptoms, psychotherapy is an available treatment option. For issues of a more intricate nature, a psychiatric consultation service is available [3].

As for the drug evidence, fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is primarily used to treat depression, anxiety, and obsessive-compulsive disorder. Its potential for use in the treatment

of COVID-19 patients has recently been suggested on the basis of its anti-inflammatory effects. When given during the active phase of infection (acute COVID-19), it reduced fatigue but did not clearly improve other symptoms [108]. Furthermore, an Italian study reported that among 60 patients who developed major depressive episodes following COVID-19 and were treated with SSRIs, 92% showed a 50% or greater reduction in Hamilton Depression Rating Scale scores after 4 weeks [109]. Clomipramine, a tricyclic antidepressant, has been suggested as a treatment for post-COVID-19 central nervous system sequelae of the central nervous system due to its anti-inflammatory properties and ability to penetrate the central nervous system. However, this has not yet been proven in RCTs [110].

8) How are sleep disorders treated in patients with PASC?

Recommendation

- Recommended treatment for sleep disorders includes sleep hygiene correction, elimination of interfering factors (habits, substances, and environment), and treatment of underlying conditions such as sleep apnea, restless legs syndrome, pain, and anxiety (G, I).
- For first-line treatment, cognitive behavioral therapy for insomnia (CBT-I), use of a sleep diary and the administration of short-term medication may be considered if indicated. In the absence of a response or the presence of complex issues, referral to a sleep medicine or mental health specialist should be considered (G, IIa).

International guidelines recommend improving sleep hygiene (limiting caffeine and alcohol, regular exercise, optimizing the bedroom environment, and limiting electronic devices) as the primary management approach [75]. The primary treatment for insomnia is CBT for insomnia (CBT-I), a multifaceted approach incorporating sleep restriction, fixed wake-up and bedtimes, strengthening the bed-sleep association, bed disengagement during anxiety, muscle relaxation, mindfulness, and meditation. In a small-scale study, online CBT and teletherapy were also effective.

A meta-analysis of non-pharmacological therapies demonstrated a significant effect of yoga, CBT, music therapy, and light therapy in improving Pittsburgh Sleep Quality Index scores. In the absence of psychiatric

disorders, medications such as melatonin, valerian, hydroxyzine, and trazodone may be used as short-term adjuncts. Due to the adverse effects and risk of dependence associated with them, benzodiazepines should be used only when strictly necessary [35, 111]. In cases where mental illness is present, treatment for that condition should be prioritized. If indicated, polysomnography and referral to a specialized sleep clinic are recommended [35].

9) How are swallowing disorders (dysphagia) treated in patients with PASC?

Recommendation

- In treating PASC-associated dysphagia, swallowing rehabilitation exercises, neuromuscular stimulation therapy, and nutritional status improvement may be attempted. Referral to a specialist in dysphagia is recommended (G, I).

Existing guidelines do not describe treatment methods for swallowing disorders specifically tailored to the unique context of patients with PASC. Instead, they mention applying general treatment methods for swallowing disorders. The guidelines for swallowing disorders developed by the Korean Academy of Rehabilitation Medicine and the Korean Dysphagia Society recommend tongue and pharyngeal muscle strengthening exercises, neuromuscular electrical stimulation, and nutritional intervention with a high level of recommendation to improve swallowing function [79].

10) How are olfactory or gustatory disorders treated in patients with PASC?

Recommendation

- Olfactory training has demonstrated efficacy in ameliorating olfactory dysfunction in patients with PASC; to date, no evidence supports pharmacologic therapy (A, I).
- Clinical application of PEA and topical corticosteroid nasal sprays may be considered with caution as adjunctive options in selected patients, as only limited and inconsistent evidence supports their use (G, IIb).

Gustatory disorders caused by COVID-19 generally improve over time, but currently, no research data is available to serve as evidence for treating gustatory

disorders. The olfactory nerve has the capacity to regenerate, meaning that olfactory impairment can be addressed through repeated olfactory training. A systematic review of RCTs evaluating the effectiveness of various treatments for olfactory disorders found that 11 out of 15 studies demonstrated benefits of olfactory training. Olfactory training was strongly recommended alongside smoking cessation advice [112]. Subsequent large-scale RCTs and multiple meta-analyses have also confirmed the significant improvement in olfactory function achieved through olfactory training [113, 114]. A classic olfactory training method involves smelling and recording four scent sources, including rose, eucalyptus, clove, and lemon, for 20–30 s each. Olfactory training is a viable option for treating patients with olfactory dysfunction due to its low cost, ease of use at home, and lack of systemic adverse events. Consultation with an otolaryngologist or with a neurologist is recommended for symptoms persisting for 3 months or longer.

Several studies have been conducted to evaluate the effectiveness of various treatments for olfactory disorders in COVID-19 patients. Among these, PEA is gaining attention as a potential therapeutic agent capable of improving neuroinflammation occurring after coronavirus infection [47]. Multiple RCTs have reported improvements in olfactory threshold, discrimination ability, and identification ability in patients with PASC [115, 116]. However, no significant effects were consistently observed when PEA was used alone without olfactory training [6]. Therefore, PEA may be considered an adjunctive therapy, as insufficient evidence supports its use as monotherapy. Efficacy of topical corticosteroid nasal sprays for treatment of olfactory dysfunction has been reported in RCTs [113, 117, 118]. However, meta-analyses have yielded conflicting results, showing no significant difference in recovery rates between olfactory training alone and olfactory training combined with steroids [113], while some RCTs reported no effect [119]. Therefore, effects of corticosteroids are inconsistent and may be carefully considered in patients who do not have contraindications to steroids. Alpha-lipoic acid, gabapentin, and vitamin A have not been demonstrated to improve olfactory function in RCTs [120–122]. Platelet-rich plasma and pentasodium diethylenetriamine pentaacetate have exhibited efficacy in some small-scale studies [12, 13], but they cannot be recommended as routine treatments due to limitations in study size and reproducibility.

11) How is PEM/PESE treated in patients with PASC?

Recommendation

- In patients with PASC presenting with PEM, education on maintaining appropriate rest and activity cycles, including pacing and symptom-titrated activity while avoiding graded exercise programs that may exacerbate symptoms, may be considered (G, IIb).

Patients without PEM or PESE can undergo physical capacity enhancement therapy to help restore their individual physical functions [123]. However, in cases presenting with PEM or PESE, a gradual increase in exercise or activity levels can cause physical and emotional harm, sometimes leading to irreversible consequences and accelerating disease progression [124]. Physicians should not force patients experiencing PEM or PESE to increase their activity levels; rather, they should encourage them to rest.

Currently, no specific treatment exists for PEM or PESE symptoms following COVID-19. According to the data, "pacing" allows patients to experience fewer symptoms, improved quality of life, and a greater likelihood of enhanced physical function and reduced fatigue severity [124]. Pacing involves accurately assessing one's physical, mental, and emotional resources, making space for uncontrollable factors, and adjusting rest and activity accordingly. What constitutes a sustainable level of activity varies from person to person, and these standards may fluctuate over time. To prevent and mitigate PEM or PESE, planning for additional rest periods before and after strenuous activities may be important. Raising awareness of daily activity levels that do not trigger a recurrence of PEM or PESE symptoms may be also helpful [125].

12) How is POTS treated in patients with PASC?

Recommendation

- Non-pharmacologic therapies and pharmacologic therapies may be considered for patients with PASC who present with autonomic nervous system dysfunction, depending on their hemodynamic status (G, IIb).

When diagnosed with POTS, non-pharmacologic therapy is prioritized [126]. However, most cases present with insufficient symptom control, necessitating consideration of pharmacologic therapy based on the hemodynamic profile of patients [127]. The non-pharmacologic and pharmacologic treatments presented in **Table 10** may be applied, with reassessments conducted at 1-2 month intervals to monitor the progress of patients.

1. Tachycardia phenotype: Ivabradine and beta-blockers (propranolol and metoprolol)
2. Hypotensive phenotype: midodrine, pyridostigmine, and droxidopa
3. Hyperadrenergic phenotype: clonidine and methyldopa

For persistent symptoms despite ongoing non-pharmacologic and pharmacologic therapies, non-invasive neuromodulation techniques may be considered as a recent treatment option [3]. Additionally, CBT, breathing retraining, and paced postural exercises that incorporate breathing have been proposed [128].

"Low-level tragus stimulation" is a noninvasive technique that stimulates the vagus nerve by applying low-level electrical stimulation to the tragus [129]. Applying electrical stimulation to specific areas of the outer ear selectively activates the afferent branches of the vagus nerve, thereby enhancing parasympathetic nerve activity and reducing sympathetic nerve hyperactivity. This method can reduce the heart rate response to the upright posture in patients with POTS and alter autonomic imbalance.

(2) Should prophylactic anticoagulants be administered to patients with PASC?

Recommendation

- Insufficient evidence exists to recommend for or against the use of anticoagulants or antiplatelet agents solely for thrombosis prevention in patients with PASC. Decisions regarding thromboprophylaxis should be individualized based on an assessment of both thrombosis risk and bleeding risk. The use of therapeutic-dose anticoagulants or antiplatelet agents for primary prevention is not recommended. In patients who report dyspnea without clear pulmonary abnormalities, diagnostic evaluation

should be performed to differentiate pulmonary artery thrombosis from deep vein thrombosis. If thrombosis is confirmed, the decision to initiate anticoagulant or antiplatelet therapy should follow established clinical guidelines (C, III).

For adult patients requiring hospitalization due to COVID-19, the use of low molecular weight heparin or unfractionated heparin is recommended [50]. However, these recommendations are limited to the acute phase treatment of COVID-19, whereas insufficient evidence to apply the same to patients with PASC. The incidence of thrombosis in patients with PASC is reported to be low at 2.5% at day 30, comparable to the incidence of complications due to bleeding [49]. A meta-analysis of cardiovascular outcomes 12 months following COVID-19 showed an additional disease burden of 2.93 cases of pulmonary embolism and 2.09 cases of deep vein thrombosis per 1,000 people. However, this increase was only significant among hospitalized patients [130]. A study analyzing the long-term

effects of thromboprophylaxis found that, compared with that in the control group, the incidence of atrial fibrillation and sudden cardiac death at 12 months was lower in the group receiving rivaroxaban for 30 days. The incidence of atrial fibrillation was 0.20% (2/996) in the treatment group and 0.99% (8/808) in the control group ($P=0.026$). The incidence of sudden cardiac death was 0.30% (3/996) in the treatment group and 2.35% (19/808) in the control group ($P<0.001$) [131]. However, another study analyzing the long-term effects of thromboprophylaxis found no significant differences in quality of life, cardiovascular events, PASC, or functional limitations after two years between the group that received enoxaparin for 14 days and the control group [132]. The studies conducted refer to an extension of the thromboprophylaxis period within 45 days. To date, long-term administration has not been evaluated [3].

Moreover, insufficient evidence exists to recommend use of anticoagulants or antiplatelet agents for more than 30 days to prevent thrombosis in patients with

Table 10. Treatments for POTS

Non-pharmacologic therapy
• Water intake: 2–3 L daily • Oral NaCl intake: 10–12 g daily • 20–40 mmHg compression garment: focusing on the abdomen and legs • Sleeping with the head elevated ($>10^\circ$) • Drinking water before getting up in the morning • Physical training: simple isometric, aerobic, and resistance exercises • Avoiding situations that may worsen symptoms: sleep deprivation, exposure to hot or warm environments, alcohol consumption or overeating, prolonged meals, standing, anemia, and dehydration • Educating that POTS is a dynamic disease and can occur after infection • Careful transition from a lying or sitting position to a standing position • Skeletal muscle pump that increases venous return and prevents fainting • Eating small, frequent meals and reducing refined carbohydrate intake • Blood sugar balance and prevention of postprandial hypotension
Pharmacologic therapy
• Vasoconstriction or increased fluid volume 1) Midodrine 2.5–15 mg three times daily 2) Droxidopa 100–600 mg every 8 h 3) Fludrocortisone 0.1–0.2 mg daily 4) Desmopressin 0.1–0.2 mg 5) Erythropoietin 10,000 IU weekly • Heart rate control 1) Ivabradine 2.5–7.5 mg every 12 h 2) Propranolol 10–20 mg daily, up to 4 tablets 3) Low-dose metoprolol • Autonomic nervous system control 1) Pyridostigmine 30–60 mg daily, up to 3 tablets 2) Clonidine 0.1–0.2 mg oral patch 3) Methyldopa 125–250 mg every 12 h • Intravenous immunoglobulin and plasma exchange
Non-invasive neuromodulation
• Low-level tragus stimulation

PASC. Therefore, whether to prevent thrombosis in patients with PASC should be determined by weighing the general risks of thrombosis and bleeding based on the underlying conditions and current status of patients. Therapeutic-dose anticoagulants are not recommended for thromboprophylaxis because no evidence suggests that they provide a greater benefit than standard doses; in addition, they increase the risk of bleeding [50]. According to the guidelines, performing tests for pulmonary embolism is necessary if dyspnea persists despite no significant abnormalities in the lung parenchyma [51].

(3) Should systemic steroids be administered to patients with PASC?

Recommendation

Systemic steroids

- The use of systemic steroids is not recommended during acute COVID-19 for the purpose of preventing subsequent PASC (G, III).
- The current body of evidence does not support the recommendation of systemic steroids for PASC. The use of systemic steroids is not recommended in the absence of specific indications (D, III).

Topical steroids - Inhaled or intranasal administration

- In the absence of clear indications such as bronchial hyperresponsiveness, inhaled steroids are not recommended for chronic cough following SARS-CoV-2 infection, and their clinical application should be considered with caution (D, III).
- The use of intranasal steroids for the purpose of improving diminished olfactory function is not recommended in patients with PASC in the absence of indications from other diseases (G, III).

Although studies indicate that nasal steroid sprays provide faster symptom improvement than no treatment [117, 118], the corresponding studies also confirm improvement in olfactory function in the control group. Current guidelines primarily recommend olfactory training to improve this symptom [35, 50]. Therefore, use of intranasal steroids for reduced sense of smell

is not recommended except in cases where clear indications exist. Additionally, although several studies have examined use of inhaled steroids in patients more than 12 weeks post-SARS-CoV-2 infection, results are inconsistent. However, no high-level studies, such as RCTs or prospective studies, are available. Therefore, use of inhaled corticosteroids for therapeutic purposes in patients with PASC and cough symptoms, but no other clear indications such as bronchial hyperresponsiveness, is not currently recommended. This is because no clear evidence supports that the benefits of these medications outweigh the risks.

One study found that, compared with that in the group that did not use steroids during the acute phase of the disease, the incidence of systemic pain and mental health abnormalities was higher among patients who received steroids 1 year later. However, this was an observational study involving only 76 patients. The study did not document the indications for steroid use during the acute phase of the disease, leaving them unclear. Furthermore, patients who died or had cognitive impairment were excluded, which introduced bias in patient selection [94], rendering the reliability of the study results very low. Therefore, insufficient evidence is available to recommend use of steroids for the purpose of preventing PASC in acute COVID-19 patients. Furthermore, the United States NIH COVID-19 clinical practice guidelines strongly recommend against the use of systemic steroids in acute COVID-19 patients who do not require supplemental oxygen and have no other clear indications [133]. Use of systemic steroids to prevent chronic forms of the disease from acute forms is not recommended due to unclear efficacy and potential adverse effects. However, no statistically significant improvements in hand strength or lung function have been observed.

Additionally, the World Health Organization mentioned the possibility of short-term, low-dose steroid use for joint pain symptoms associated with PASC [50]. However, no evidence has been identified to support the generalization of such steroid use. Additionally, no studies demonstrate a benefit from systemic steroid use in patients with PASC who do not have an objective disease condition confirmed to be steroid-responsive (e.g., post-COVID organizing pneumonia, inflammatory interstitial lung disease, and rheumatologic disease) as of now. Therefore, the use of systemic steroids is not recommended in patients with PASC.

(4) Should anti-fibrotic drugs be administered to patients with PASC?

Recommendation

- The treatment of PASC-associated pulmonary fibrosis involves the use of diagnostic procedures such as chest CT, which provide crucial information to evaluate the extent of pulmonary fibrosis (A, I).
- In patients with severe COVID-19 and confirmed pulmonary fibrosis, antifibrotic agents (pirfenidone or nintedanib) are recommended, after appropriate radiologic confirmation and assessment of comorbidities (A, I).
- The selection of antifibrotic agents should be based on a comprehensive evaluation of the underlying lung disease, and this decision should be made in consultation with a pulmonologist (A, I).

Prior to administering antifibrotic agents, the presence of pulmonary fibrosis following PASC should be confirmed using methods such as chest CT, and the degree of pulmonary fibrosis (pulmonary fibrosis score) should be assessed. When selecting antifibrotic agents, identifying any underlying lung disease or comorbidities is important [47, 134]. In most RCTs, use of antifibrotic agents showed positive results in improving lung function (forced vital capacity and diffusing capacity), the 6-min walk test, and survival rate [95, 135-137].

(5) Is respiratory rehabilitation therapy necessary for patients with PASC?

Recommendation

- General rehabilitation and respiratory rehabilitation are recommended for patients with PASC. This recommendation is supported by multiple RCTs demonstrating that these interventions are effective in improving a range of PASC-related symptoms (A, I).

Several RCTs conducted in different countries, along with multiple meta-analyses and systematic reviews, have examined the efficacy of general respiratory rehabilitation therapy in patients with PASC. Representative studies are as follows. From January 2020 to February 2023,

Pouliopoulou et al. conducted a meta-analysis and systematic review of 14 RCTs examining the effects of various rehabilitation programs (e.g., breathing exercises and exercise-based rehabilitation therapy) on 1,244 patients with PASC. Patients who underwent rehabilitation therapy consistently demonstrated significant improvements in exercise capacity (measured by the 6-min walk test), dyspnea, and quality of life. However, the need for monitoring potential adverse events during exercise was emphasized [46].

Deng et al. conducted a meta-analysis and systematic review of 11 RCTs involving rehabilitation interventions and comparison groups for patients aged 60 years or older with PASC, published in PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Library databases up to November 2023. A total of 832 participants were included. The rehabilitation intervention resulted in an average increase of 15.77 m (95% CI, 5.40-26.13; $P<0.01$) in the 6-min walk test and 4.11 repetitions (95% CI, 2.46-5.76; $P<0.001$) in the 30-s stand-up test, demonstrating significant improvement in each measure. Significant effects were found regarding improvement in quality of life and independence in daily living (standardized mean differences [SMD] = 0.31, 95% CI, 0.14-0.48; $P<0.001$), as well as alleviation of fatigue (SMD = -0.66, 95% CI, -1.13 to -0.19; $P<0.01$), depression (SMD = -0.89, 95% CI, -1.76 to -0.02; $P<0.05$), and anxiety (SMD = -0.81, 95% CI, -1.58 to -0.05; $P<0.05$). However, no statistically significant improvements in hand strength or lung function were evident [138].

In addition, Romanet et al. conducted a meta-analysis and systematic review of clinical studies that implemented respiratory rehabilitation therapy for adults with dyspnea due to PASC, regardless of the severity of initial symptoms, up to July 2023, using the MEDLINE (National Library of Medicine's premier bibliographic database), PEDro (Physiotherapy Evidence Database), WOS (Web of Science), Scopus, VHL (Virtual Health Library), and Cochrane Library databases. A total of 19 studies (15 RCTs and four non-RCTs) involving 1,292 adults were included. These comprised six studies of respiratory muscle training, six of low- to moderate-intensity rehabilitation, six of high-intensity rehabilitation, and one of passive rehabilitation. Significant differences in rehabilitation methods were observed between and within groups and high heterogeneity was present; nonetheless, the random-effects model indicated that rehabilitation therapy effectively alleviated dyspnea in patients.

However, given the variability in rehabilitation methods across studies and the presence of discrepancies in the results, a need exists for more systematic and consistent research [139].

In Egypt, 60 patients with diaphragmatic dysfunction due to PASC were randomly assigned to one of three groups for an 8-week intervention: standard treatment alone, standard treatment plus incentive spirometry training, or standard treatment plus diaphragmatic breathing training. Patients in the incentive spirometry and diaphragmatic breathing groups experienced significant improvement on the modified Medical Research Council (mMRC) dyspnea scale [140].

In addition, a RCT from Egypt enrolled 68 patients aged 40–70 with PASC who reported dyspnea, fatigue, and exercise intolerance. Over 12 weeks, the rehabilitation group received conventional medical care in combination with a home-based pulmonary rehabilitation exercise program, while the control group received conventional medical care alone. The Physical Fitness Index (PFI), Chalder Fatigue Scale, Short Form 36 Health Survey Questionnaire (SF-36), Dyspnea Scale, and 6-min walk test scores were assessed before and after the 12-week intervention. The rehabilitation therapy group showed a significant decrease in the Chalder Fatigue Scale (11.1 ± 0.94) score, with significant increases in the 6-min walk test (439.7 ± 25.3) and the PFI (52.3 ± 10.2) scores. The SF-36 survey score was also higher in the rehabilitation group (66.4 ± 3.7), and the mMRC dyspnea score showed significant improvement in the rehabilitation group (26.7% dyspnea stage 2, 63.3% stage 1, 10% stage 0, $P < 0.001$) [141].

In another study, a Spanish RCT randomly assigned 64 patients with PASC experiencing dyspnea and fatigue to two groups (aerobic exercise plus home-based inspiratory muscle and respiratory muscle training, or aerobic exercise alone) for an 8-week intervention. The participants performed 50 min of aerobic exercise twice a week and 40 min of muscle training three times a week. The primary endpoints were quality of life assessed via the EuroQol-5D questionnaire and exercise tolerance measured through cardiopulmonary exercise testing. Secondary endpoints included inspiratory and expiratory muscle strength, inspiratory muscle endurance, upper and lower limb muscle strength, spirometry, pulmonary diffusion capacity, and levels of anxiety and depression. The group that underwent muscle training after rehabilitation showed significant improvement in inspiratory and expiratory muscle function, as well as

moderate improvement in peak expiratory flow rate. However, no statistically significant differences were observed in quality of life or exercise tolerance [142].

Another Spanish RCT enrolled 220 patients experiencing persistent dyspnea, fatigue, and olfactory and gustatory disorders for over 5 months post-COVID-19 diagnosis. One hundred patients were assigned to an intervention group combining inspiratory muscle training, aerobic exercise, and olfactory and gustatory training. The remaining 100 patients served as a control group receiving no additional treatment. The 31-day treatment period yielded statistically significant improvements in the intervention group compared to the control group for lung capacity (forced vital capacity, FVC), lung function indicators (FEV1/FVC ratio), peak inspiratory pressure, and dyspnea (modified Borg scale and mMRC scale). The olfactory and gustatory surveys also indicated a marked improvement following treatment [114].

Multiple RCTs, meta-analyses, and systematic reviews strongly recommend general and respiratory rehabilitation as treatment for PASC. In Korea, rehabilitation medicine specialists should determine the type and duration of rehabilitation therapy for various PASC symptoms based on the accessibility of such therapy.

6. PREVENTION

(1) What are the strategies that can effectively prevent PASC?

1) Can antiviral treatment administered for the purpose of treating COVID-19 reduce the risk of developing PASC?

Recommendation

- Early antiviral treatment in the initial phase of SARS-CoV-2 infection may help reduce the risk of developing PASC and the resulting hospitalization and death (B, I).
- The use of antiviral agents for therapeutic purposes in patients with established PASC is not recommended (A, I).

Early administration of antiviral drugs may help prevent PASC. A meta-analysis of observational studies showed that early antiviral treatment significantly reduced the risk of developing PASC (27.5%; 95% CI, 25.3–59.1) compared with the untreated group [17]. Furthermore,

early administration of antiviral drugs lowers the likelihood of PASC-related hospitalization and death [17]. A study by Chilunga et al. included in the meta-analysis found no statistically significant preventive effect in the group administered remdesivir [143]. However, a study by Xie et al. reported a significant preventive effect of molnupiravir against PASC [144]. The benefits of early antiviral treatment were demonstrated in three out of four observational studies evaluating the efficacy of nirmatrelvir and ritonavir. The recent RANORAMIC trial revealed that, for high-risk COVID-19 patients, administering molnupiravir within 5 days of symptom onset reduced the rate of persistent symptoms at 6 months by 2.5% [145]. Additionally, administration of ensitrelvir during the early acute phase has been reported to potentially reduce the risk of developing some symptoms of PASC [146]. To date, only two RCTs have administered antiviral drugs for treatment purposes after the onset of PASC symptoms: the STOT-PASC trial and the PAX-LC trial. Neither study confirmed a significant difference between the nirmatrelvir/ritonavir group and the control group [147, 148].

In summary, the potential for antiviral administration during the acute phase of SARS-CoV-2 infection (within 5 days of symptom onset) to reduce the occurrence of PASC has been consistently observed in observational studies and meta-analyses. However, these studies are limited by the inherent constraints of observational research. Conversely, the therapeutic approach of administering antiviral drugs after the onset of PASC has not demonstrated significant benefits in current RCTs. Therefore, well-designed RCTs are warranted to provide definitive recommendations.

The mechanism by which early antiviral treatment prevents PASC is not yet fully understood. One hypothesis is that the SARS-CoV-2 virus causes prolonged, persistent inflammation in the body, resulting in PASC [8]. From this perspective, the presumption is that early antiviral agents contribute to improving COVID-19-related symptoms and reducing the occurrence of PASC by suppressing viral replication within the body and reducing the viral load.

2) Can COVID-19 vaccination reduce the risk of developing PASC?

Recommendation

- COVID-19 vaccination is recommended to reduce the risk of developing PASC (A, I).

Even in cases of breakthrough infection, receiving the COVID-19 vaccine provides a preventive effect against PASC. A meta-analysis of six observational studies demonstrated that even a single vaccination dose significantly reduced the risk of PASC compared with the risk in unvaccinated individuals, with an odds ratio of 0.539 (95% CI, 0.295–0.987) [149]. Other meta-analyses found that the group that received two primary doses had an odds ratio of 0.64 (95% CI, 0.45–0.92) compared with the unvaccinated group. The group that received one dose had an odds ratio of 0.60 (95% CI, 0.43–0.83), which indicated an effect in preventing PASC [150]. Therefore, COVID-19 vaccination is necessary to prevent PASC. The mechanism by which COVID-19 vaccination prevents PASC is not yet fully understood. However, theoretically, the purpose of vaccination is to enable the rapid elimination of the virus within the body upon a breakthrough infection. Furthermore, the belief is that vaccination can reduce the acute immune response to mitigate tissue damage and improve immune dysregulation, thereby decreasing the risk of secondary autoantibody production.

A meta-analysis evaluating the effectiveness of COVID-19 vaccination in patients with PASC found that vaccination reduced the odds ratio for symptom persistence to 0.73 (95% CI 0.57–0.92), decreasing the likelihood of symptom persistence by 27% compared with that in the unvaccinated group [151]. However, this analysis had several limitations. The high heterogeneity among the studies included in the analysis limited the reliability of the results, which may have been due to recall bias or the potential for recovery based on the natural course of symptoms. Furthermore, certain studies have indicated an absence of clarity concerning whether vaccination occurred subsequent to the diagnosis of PASC. Regarding safety, no serious adverse events were reported in association with vaccination in the meta-analysis.

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Conflict of Interest

JYS is on the editorial board of *Infection & Chemotherapy*; however, he was not involved in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article were reported.

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, TK, 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, TK, SHL, EL, YBS, YJ, YHJ, YJC. Writing - review & editing: JWS, EJK, YBS, JYS.

SUPPLEMENTARY MATERIAL

Supplementary Material

Korean version

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