Recent update on long COVID syndrome: Immunopathogenesis and clinical consequences

Gatot Soegiarto¹², Kenneth Martino Djajapranata³⁴

ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic with millions of confirmed cases. Despite the majority of patients recovered from the acute infection, a subset of individuals experiences persistent symptoms known as long COVID, creating a distinctive clinical entity. Immunopathogenesis emerges as a central player in the intricate web of long-term COVID, involving chronic inflammation, autoantibody formation, and sustained viral presence. The syndrome manifests across diverse organ systems, with neurological, cardiovascular, and musculoskeletal implications. Prolonged lung damage and neurological sequelae significantly contribute to the broad spectrum of symptoms observed, ranging from dyspnea to cognitive impairment. Although the understanding of long COVID continues to evolve, navigating the epidemiology of long COVID remains challenging due to varied definitions and study populations among published studies. In addition, various risk factors, encompassing age, gender, comorbidities, and initial COVID-19 symptomatology, further contribute to the complexity of long COVID. Therefore, this review aims to comprehensively explore long COVID in terms of its definition, epidemiology, recent insights into immunopathogenesis, clinical manifestations, underlying mechanisms, and possible management of long COVID syndrome.

Keywords: Long COVID, immunopathogenesis, clinical manifestations, organ damage.


INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread widely throughout the world. More than 657 million confirmed cases and over 6.67 million deaths have been reported globally in early January 2023.¹ Despite the majority of COVID-19 patients have recovered, with an average global case fatality rate ranging from 2-3%,² a subset of individuals experiences persistent symptoms referred to as long COVID or post-COVID syndrome.³⁴ The number of long COVID cases appears to progressively increasing although their actual incidence and prevalence could not precisely estimated due to varying rates reported in different publications.⁵

Long COVID has a wide variety of symptoms that must be carefully identified for accurate diagnosis. Generally, these symptoms are categorized into two types: general or systemic symptoms (e.g. fatigue, headache, and fever) and symptoms specific to organ systems such as respiratory, nervous, cardiovascular, coagulation, and gastrointestinal systems. Individuals with long-term COVID exhibit disruption in the structure and function of various organs, resulting in diverse symptoms.⁶ However, the duration of long COVID does not necessarily correlate with the severity of the initial COVID-19 or the duration of its symptoms.⁵

Understanding the pathogenesis of long COVID is challenging due to its highly variable clinical spectrum and its impact on multiple organs. The prevailing belief is that the pathogenesis is multifactorial, involving more than one mechanism contributing to various clinical manifestations, with long-term inflammation playing a pivotal role.⁷ Given its emergent and complex nature, gaining a better understanding of the mechanisms behind long COVID is crucial, as it provides guide for further research and potential therapeutical strategies. Therefore, the aim of this review was to provide a brief overview of the definition, epidemiology, recent developments in immunopathogenesis, clinical manifestations, and management of long COVID syndrome.

Definition and Epidemiology

The term long COVID was first introduced by Perego in a tweet on social media, describing the persistence of various symptoms or the emergence

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of several new symptoms that last several weeks or months after the resolution of the acute SARS-CoV-2 infection, irrespective of virulence status. Long COVID is also known as post-COVID-19 syndrome. Long COVID is categorized into two types based on the duration of its symptoms, namely post-acute COVID-19 and chronic COVID-19 (Figure 1). The first condition is designated when the symptoms persist for more than 3 weeks, but less than 12 weeks after the onset of the disease, whereas the later condition is diagnosed when the symptoms continue to exist for more than 12 weeks.

Numerous alternate expressions are used to describe long COVID. These include long haul COVID, post-acute COVID-19, post-COVID syndrome, post-acute sequelae of SARS-CoV-2 infection (PASC), long-term effects of COVID, or chronic COVID. Several organizations such as the American Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and NICE employ slightly different definitions. CDC describes long COVID as signs, symptoms, and conditions persisting or emerging after COVID-19, manifesting four weeks or more after acute infection. These manifestations are multisystemic, recurring or worsening, potentially becoming severe or life-threatening several months or even years after the initial infection. WHO characterizes it as persistent symptoms or the emergence of new symptoms three months following the initial SARS-CoV-2 infection, lasting at least two months and not attributable to other causes. NICE defines long COVID as the presence of signs and symptoms that develop during or after the onset of the disease, enduring more than four weeks and not explicable by other diagnoses. Several clinical categories and screening parameters have been proposed for the identification of COVID-19 sequelae in long COVID patients (Table 1).

It is difficult to accurately estimate the epidemiology of long COVID syndrome, both in hospitalized and outpatient settings, due to the heterogeneity among studies in terms of diagnostic definitions, populations, as well as follow-up times and types. Various studies with different follow-up durations have reported diverse incidence rates of long COVID, ranging from 32.6% to 87.0% after two months, 96.0% after three months, and 76.0% after six months. However, a meta-analysis study and systematic review of 41 published reports suggested an approximately 43.0% global prevalence of long COVID, with 54.0% rate for hospitalized and 34.0% for non-hospitalized individuals. Regionally, Asia exhibits the highest prevalence (51.0%), followed by Europe (44.0%) and the United States (31.0%).

**Immunopathogenesis of Long COVID**

The immunopathogenesis of long COVID has not been fully understood since different mechanisms may occur in each infected individual, causing different conditions among sufferers. Current evidence suggests that prolonged inflammation plays a pivotal role in the pathogenesis of various clinical manifestations associated with long-term COVID. Other mechanisms might include sequelae owing to organ damage, different recovery times for each damaged organ, persistence of chronic inflammation, development of autoantibodies, prolonged presence of the virus or its components in the body leading to dysbiosis, nonspecific effects arising from hospitalization (e.g. sequelae of critical illness and post-intensive care syndrome), complications related to SARS-CoV-2 infection or comorbidities, adverse effects of therapy, reactivation of infection associated with other viruses (e.g. HSV-human simplex virus, HHV-human herpesvirus, EBV-Epstein-Barr virus, CMV-cytomegalovirus), microvascular dysfunction, coagulation disorders, deconditioning, and psychological issues

**Table 1. Clinical categories and screening parameters for the sequelae of COVID-19**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory examination</td>
<td>Confirmed history of COVID-19 infection through reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab examination and/or antibody examination. The presence of abnormal laboratory findings.</td>
</tr>
<tr>
<td>Radiology</td>
<td>The presence of pathological findings on computed tomography (CT) scan or chest radiograph compared to initial examination.</td>
</tr>
<tr>
<td>Deterioration of functional status</td>
<td>Deterioration of functional status as compared to initial examination values.</td>
</tr>
<tr>
<td>Subjective symptoms and quality of life parameters</td>
<td>New or worsening symptoms of more than 2 weeks since the onset. Duration or return of the symptoms is more than 2 weeks compared to the initial assessment.</td>
</tr>
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</table>
Many studies suggested that SARS-CoV-2 remains positive in the body of COVID-19 patients for more than 3 months after the onset of the illness. This prolonged inflammation may be linked to the gastrointestinal tract, where SARS-CoV-2 efficiently replicates in the gastric and intestinal cells due to a high expression of ACE2 receptor. The viral nucleic acids and proteins can linger in the small intestine of asymptomatic COVID-19 patients for up to four months, and the virus itself is detectable in feces for up to two months. The prolonged presence of SARS-CoV-2 stimulates immune system activation, contributing to gastrointestinal manifestations and long COVID. Systemic inflammation may occur as a result of inflamed intestinal mucosa, enhancing bacterial translocation and sustaining a prolonged activation of immune responses. Patients with long COVID may also experience gut dysbiosis persisting for up to 30 days post-recovery.

Increased Ruminococcus gnavus and Bacteroides vulgatus, and decreased Faecalibacterium prausnitzii population were detected. A study found that the presence of pathogenic germs in the gastrointestinal tract was correlated to persistent respiratory symptoms, whereas colonization by nosocomial germs such as Clostridium innocuum and Actinomyces naeslundii was associated with neuropsychiatric symptoms and fatigue.

Multisystem inflammatory syndrome owing to COVID-19 infection can trigger reactivation of infections by several other viruses such as HSV, EBV, HHV-6, HHV-7, varicella zoster virus (VZV), and cytomegalovirus (CMV). This condition, in turn, contributes to a prolonged systemic inflammation, causing damage to body tissues and triggering the release of self-generated neoantigens. As a result, it leads to a potential activation of autoreactive T cells through the activation of bystander or molecular mimicry. Autoreactive B cells are another factor generating autoimmunity in long COVID sufferers through the production of various autoantibodies which target body tissue, cells, and proteins.

Pathological inflammation

Long COVID may also experience gut dysbiosis persisting for up to 30 days post-recovery. Increased Ruminococcus gnavus and Bacteroides vulgatus, and decreased Faecalibacterium prausnitzii population were detected. A study found that the presence of pathogenic germs in the gastrointestinal tract was correlated to persistent respiratory symptoms, whereas colonization by nosocomial germs such as Clostridium innocuum and Actinomyces naeslundii was associated with neuropsychiatric symptoms and fatigue.

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Numerous studies have been carried out to determine factors contributing to an increased risk of developing long COVID. Despite miscellaneous findings were observed among studies, several consistent risk factors have been identified. Being female, older age (particularly middle-aged and elderly), ethnic minorities in the US (e.g. Afro-Caribbean, Native American Indian, Middle Eastern or Polynesian ethnicities, and mixed ethnicity), having more than five COVID-19 symptoms during the initial infection (including respiratory symptoms), having specific comorbidities (e.g. hypertension, obesity, mental health disorders, immunosuppressive conditions, the presence of autoantibodies, a history of asthma, and a history of prior infection with EBV or HSV viruses), suffering from gut dysbiosis, smoking, lack of physical activity, low socioeconomic status, and completeness of vaccination status are among factors associated with an increased risk of long COVID.

Clinical Manifestation, Possible Mechanisms, and Potential Therapy
Researchers have identified various symptom patterns in individuals with long-term COVID, encompassing respiratory, neuropsychiatric, cardiac, and musculoskeletal symptoms. Diverse clinical spectrums of long COVID indicate the implication of multiple causes and mechanisms. Here, we elucidated the most prevalent symptom patterns in long COVID, along with the explanations of potential underlying mechanisms and therapies.

Respiratory symptoms
Dyspnea and pulmonary fibrosis
Shortness of breath or dyspnea is a common complaint among long COVID sufferers. The UK National Statistical data indicated that 4.6% of individuals experience dyspnea five weeks after the diseases onset. Direct damage to the lungs and airways occurs due to the viral replication in endothelial cells, causing endothelial damage and severe inflammation, which in turn leads to dyspnea. Additionally, prolonged exposure to supplemental oxygen may exacerbate lung conditions.
due to the increment of oxidative stress, consequently leading to the activation pulmonary fibrosis pathway.\textsuperscript{57} Individuals with pre-existing lung conditions are more susceptible to fibrotic changes in the lung tissue.\textsuperscript{58}

Pulmonary fibrosis, one of the most common sequela after COVID infection, has been reportedly associated with an increased levels of cytokine levels such as tumor necrosis factor-α (TNF-α) and transforming growth factor-β1 (TGF-β1),\textsuperscript{59,60} which was similar to the associated factors in individuals with dyspnea (i.e. interleukin-6 (IL-6) and TGF-β).\textsuperscript{46,61} Other factors including the impact of acute respiratory distress syndrome (ARDS) during the acute phase, direct injury to pulmonary alveoli associated with the application of mechanical ventilation, and the direct influence of the virus on the formation of fibrotic tissue have also been suggested to contribute to pulmonary fibrosis in long COVID sufferers.\textsuperscript{62} This persistent COVID condition may become more complicated in the patients experiencing the incidence of pulmonary vascular thromboembolism during their COVID-19 illness.\textsuperscript{58}

Hypothetically, aside from lung lesions, inappropriate regulation of ventilation due to autonomic nervous system disorders (damage to intrathoracic reflex receptors or brain stem zones) could also contribute to respiratory issues.\textsuperscript{63–65}

The mechanism of long COVID in the lungs is illustrated in Figure 4. Chronic inflammation initiates the prolonged production of reactive oxygen species (ROS) and pro-inflammatory cytokines (A). Subsequent endothelial damage can lead to the activation of fibroblasts and deposition of collagen and fibronectin (B). Endothelial damage, complement and platelet activation, cytokine release, coagulation pathway abnormalities, and hypoxia contribute to hyperinflammation and hypercoagulation, increasing the risk of thrombosis (C).\textsuperscript{15}

In patients whose CT scan results shows significant ground glass opacity, a typical radiological characteristic of COVID-19 pneumonia, and experience hypoxia after hospital discharge, therapy may involve administration of steroids at a dose not exceeding 20–30 mg of prednisolone, with gradual reduction based on the patient’s response.\textsuperscript{66} It is important to note that prednisolone administration may exacerbate hyperglycemia and contribute to proximal myopathy, hindering patient mobility and rehabilitation.\textsuperscript{67} In terms of dyspnea, NICE suggested a multidisciplinary approach for its therapeutic management, including certain types of rehabilitation.\textsuperscript{68} This rehabilitation include breathing exercises to regulate breathing patterns and enhance the effectiveness of respiratory muscles, especially the diaphragm, and daily aerobic and gentle breathing exercises (e.g. inhaling through the nose and exhaling through the mouth) for 5–10 minutes.\textsuperscript{69,70} A study suggested that breathing exercises could improve lung function and overall quality of life.\textsuperscript{71}

**Neuropsychiatric symptoms**

SARS-CoV-2 gains entrance to the central nervous system (CNS) through either hematogenous or retrograde neuronal pathways. The virus can disrupt the permeability of the blood-brain barrier, allowing cytokines to enter the CNS and trigger neuroinflammation.\textsuperscript{72} Some studies evidenced the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF), confirming the viral neuro-invasive characteristics, which may disrupt the brain’s microstructure in recovered COVID-19 patients.\textsuperscript{73,74} Another study suggested that the virus can induce septic encephalopathy, exerting immunological and non-immunological effects such as adaptive autoimmunity, microglial activation, and maladaptive cytokine profiles.\textsuperscript{75}

The repercussions of COVID-19 on the brain and nervous system include anosmia, venous thromboembolism (pulmonary embolism, heart attack, stroke), and cognitive disorders such as memory and concentration problems. The pandemic also adversely affects mental health, with COVID-19 patients exhibiting long-term psychiatric symptoms post-recovery, such as post-traumatic stress disorder (PTSD), depression, anxiety, obsessive-compulsive symptoms, and sleep disorders.\textsuperscript{31,76–79}

In the realm of mental health and neuropsychiatry, COVID-19 is linked to fatigue, brain fog, myalgia, headaches, anxiety, depression, posttraumatic stress disorder, and sleep disturbance.\textsuperscript{80}

**Fatigue**

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), considered one of the most common manifestations of long COVID, entails several symptoms including fatigue, post-physical activity malaise, sleep disturbances, cognitive impairment, and non-provocative pain that may persist for over six months after the infection.\textsuperscript{81} A study reported that 55.2% of long COVID sufferers reported chronic fatigue as their primary complaint.\textsuperscript{82} This condition may arise from various factors including immunological, virological, endocrinological, psychological, neurological (both central and peripheral), and pandemic-associated social aspects (Figure 5).\textsuperscript{81,83–85} The activation of cellular immunity, increased secretion of inflammatory mediators, and dysregulation of T and B cells are among considerably potential contributors to chronic fatigue in association with immunological aspect.\textsuperscript{86} Another investigation found that elevated neurofilament light chains, a biomarker of brain injury, may linger in COVID-19 patients, which in turn leads to the development of this chronic condition.\textsuperscript{8,87} Decreased metabolism in the frontal lobes and cerebellum has also been implicated to cause chronic fatigue; however, this event does not occur through a direct viral neuro-invasion pathway, but rather by systemic inflammation and cellular immune mechanisms.\textsuperscript{88,89} Furthermore, lymphatic system congestion and the accumulation of certain toxins in the central nervous system can impede the flow of cerebrospinal fluid through the cribriform plate, potentially contributing to fatigue symptoms following COVID-19.\textsuperscript{85} Nevertheless, fatigue management in individuals with long COVID remains challenging, both for patients and healthcare workers due to the absence of a definitive diagnostic method.\textsuperscript{90}

**Brain fog**

SARS-CoV-2 enters the brain through the olfactory tract and reaches the hypothalamus, activating mast cells in the brain and inducing microglia to
release pro-inflammatory molecules that contribute to brain inflammation and brain fog (Figure 6).91 The term ‘brain fog’ denotes a cluster of cognitive issues such as blurred thinking, confusion, forgetfulness, difficulty concentrating, slow thinking, and mental fatigue.91 Decreased metabolisms in the patient's brain is another critical factor associated with brain fog incidence in patients with long COVID.88,92,93 Microglia play a significant role in the inflammation and are activated by damage-associated molecular patterns (DAMPs) found in COVID-19 sufferers.94,95 The interaction of microglia with the immune cells such as mast cells in the hypothalamus can trigger impaired cognitive function.96-99 Excessive systemic inflammation during a cytokine storm triggered by SARS-CoV-2 infection, accompanied by glial cell activation, also increases the risk of other neurological manifestations such as encephalitis and stroke.100 Various clinical manifestations, including headaches, tremors, and impaired attention and concentration, may also occur in long COVID sufferers.101,102

Since one of the primary causes of long COVID is mast cell activation syndrome (MCAS), which initiates a cascade of inflammatory responses that trigger allergies, the treatment of this syndrome mainly involves the use of histamine antagonists.103-106 A study suggested that 26 patients with long-term COVID symptoms showed improvement in terms of fatigue, dyspnea, chest pain, neuropsychiatric symptoms, and skin issues (e.g. urticaria) after receiving antihistamine therapy.107

Cardiovascular and coagulation symptoms
Cardiovascular is another commonly lingering affected organ system by COVID-19, leading to various conditions such as palpitation, dyspnea, chest pain, heart muscle damage, and heart failure. Other sequelae include myocardial fibrosis, arrhythmia, tachycardia, and autonomic dysfunction due to excessive inflammation of the heart. A study reported that 86% of post-COVID-19 patients experienced cardiovascular symptoms, with 68.8%, 61.4%, and 53.1% experiencing palpitations, tachycardia, and chest pain, respectively. Cardiovascular symptoms are commonly found within the first two months post-COVID; however, some respondents also experienced symptoms of palpitations for up to 6 months and chest pain for up to 7 months following the infection.14 Several factors have been thought to contribute to persistent post-COVID-19 symptoms in the cardiovascular system. These include direct viral invasion, high expression of the ACE-2 receptor in the heart, inflammation, and immunological responses that affect the structure of the myocardium, pericardium, and its conduction system.6,85

Postural orthostatic tachycardia syndrome (POTS)
Several patients with post-COVID-19 may develop POTS.106 POTS is recognized as an autonomic nervous disorder that can persist for over six months in the patients after initial infection with SARS-CoV-2. This condition has been associated with autoimmune body production due to the viral infection, which then interacts with G protein-coupled receptors, leading to autonomic nervous dysfunction.106-108 POTS is diagnosed by an increased heart rate of >30 times per minute within the duration of 5–10 minutes while the patient stands upright without orthostatic hypotension,108 along with other symptoms such as dizziness, headaches, palpitations, blurred vision, weakness, fatigue, gastrointestinal problems, chronic pain, and sleep disorders.5,106,110-113 Non-pharmacological therapies such as increased fluid and salt intake, as well as avoiding prolonged standing, dehydration, physical activities, and wearing compression socks are recommended as the first-line therapy.114-117 However, when non-pharmacological treatment is deemed inadequate, pharmacological therapies should be given, NICE has recommended β-blockers for patients with complaints of chest pain, arrhythmias, and acute coronary syndrome.117,118 A study suggested that administering low doses of β-blockers can reduce heart rates and improve POTS symptoms.121

Endothelial dysfunction and thromboembolism
Approximately 0.8-5% of post-acute COVID-19 patients experience thromboembolic events.122 Coagulopathy may occur as a result of pathological responses to myocardial injury and myocarditis, leading to endothelial damage and microthrombosis.8,123-125

Thromboinflammation triggers complement activation, cytokine release, hypoxia, and hypercoagulation that lead to thrombosis (Figure 4).4,126-128 Treatment of venous thromboembolism (VTE) is indicated for COVID-19 patients with suspected pulmonary embolism, acute coronary syndrome, or those requiring intensive care. Direct oral anticoagulants (DOAC) and low molecular weight heparin (LMWH) can reduce VTE risk, and individuals at risk may receive extended prophylaxis for up to 45 days.127,128

Musculoskeletal symptoms
Myalgia and myopathy
Individuals with long COVID also commonly experience musculoskeletal pain.129,130 The prevalence of myalgia and arthralgia in long COVID sufferers ranges from 5.65-18.1% and 4.6-12.1%, respectively.131 Long COVID mechanisms in musculoskeletal system involve cellular immunity, cytokines, prolonged inflammation, and hyperactivation of immune cells.128,131,132 Several studies show similarities in the pathogenesis of musculoskeletal pain in long COVID sufferers and ME/CFS.131,133

Despite still being controversial, non-pharmacological therapies such as cognitive behavioral therapy (CBT) and graded exercise therapy (GET) may be used for the treatment of these musculoskeletal symptoms.135 On the other hand, NSAID drugs such as ibuprofen can be given as pharmacological therapy.136 Patients generally experience disability that may interfere with their work, daily activities, and social life, leading to depression and reduced quality of life.137,138 Thereby, antidepressants, particularly tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI), may be considered whenever clinically indicated in order to improve sleep quality and reduce pain.135,136

Management of Long COVID
Patients with long COVID should undergo a thorough and holistic assessment to identify their condition

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REVIEW


845
The emergence of new ones. Immunological continuation of acute symptoms or the status. This condition may involve the infection, regardless of the virulence for weeks or months after SARS-CoV-2. Long COVID syndrome, also known in inflammatory effects of vitamin C make antiviral, antioxidant, and anti-folate in particular, and vitamin C promote and prevent organ damage. The antiviral, antioxidant, and antiproliferation treatments. Oxygen supplementation is given to patients experiencing difficulty breathing. While there is no evidence supporting the effectiveness of corticosteroids for the treatment of long-term COVID, inhaled corticosteroids may be administered to mitigate prolonged inflammation, such as coughing or wheezing. Food supplements have the potentials to mitigate prolonged inflammation, reduce free radicals, increase energy intake, improve mitochondrial function, and prevent organ damage. Thiamine, vitamin C, and vitamin D have been proven beneficial for COVID-19 sufferers, ARDS, and sepsis. Vitamin B, such as folate in particular, and vitamin C promote detoxification and enhance immune function by regulating inflammation. The antiviral, antioxidant, and anti-inflammatory effects of vitamin C make it a potential therapeutic option for long COVID.

CONCLUSIONS

Long COVID syndrome, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is characterized by the presence of various symptoms persisting for weeks or months after SARS-CoV-2 infection, regardless of the virulence status. This condition may involve the continuation of acute symptoms or the emergence of new ones. Immunological mechanisms play a crucial role in the increased incidence of long COVID, including immune response deviation, viral replication persistence, formation of amyloid fibrin micro clots resistant to fibrinolysis, acute damage to one or more organs owing to SARS-CoV-2 infection, and generation of various autoantibodies. Upon entering the body, SARS-CoV-2 binds to ACE-2 receptors found in various cells and organs throughout the human body, including the oral and nasal mucosa, lungs, heart, gastrointestinal tract, liver, kidneys, spleen, brain, and blood vessel endothelial cells. This diverse distribution explains the wide range of clinical manifestations, encompassing symptoms such as fatigue, shortness of breath, cardiovascular issues, as well as cognitive impairment and mental health issues. Effective management necessitates a tailored approach involving both pharmacological and non-pharmacological interventions.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

ETHICAL CONSIDERATION

Not applicable.

AUTHORS CONTRIBUTION

All authors contributed equally to the article preparation and publication.

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REFERENCES


