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Fatigue and Cognitive Dysfunction in COVID-19 Patients: a Narrative Review

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1. Abbreviations

AT	Angiotensin
ACE2	Angiotensin-converting enzyme 2
COVID-19	Coronavirus
CCL11	CC-chemokine ligand 11
Chronic fatigue syndrome	CFS
CNS	Central nervous system
CSF	Cerebrospinal fluid
HBOT	Hyperbaric oxygen therapy
Myalgic encephalomyelitis	ME
MLD	Manual Lymphatic Drainage
SARS-Cov-2	Severe acute respiratory syndrome coronavirus type 2
(r)TMS	(repetitive)Transcranial magnetic stimulation
TME	Toxic Metabolic Encephalopathy
WHO	World Health Organization

2. Summary

The COVID-19 pandemic, which began in Wuhan, China, in 2019, has led to significant global health crises, with widespread transmission and high mortality rates. Despite substantial vaccination efforts, the impact of COVID-19 on public health discourse persists due to its long-term effects on survivors, particularly regarding cognitive dysfunction and fatigue. Studies revealed that many COVID-19 survivors experience severe physical impairment for up to 20 months post-infection, with symptoms including dyspnea, fever, myalgia, and fatigue. Post-COVID-19, characterized by a range of symptoms that persist beyond the acute phase of the illness, affects around 10-15% of infected individuals, negatively impacting their quality of life. Research suggests several potential mechanisms underlying the neurological symptoms observed in COVID-19 patients. These include direct viral invasion of the central nervous system, immune dysregulation triggering neuroinflammation, endothelial dysfunction leading to vascular damage, and the effects of severe systemic COVID-19 on the central nervous system. Studies have shown elevated levels of SARS-CoV-2 spike protein in post-COVID patients, indicating ongoing viral activity. Moreover, ACE2 expression in the brain suggests potential routes for viral entry, such as the olfactory nerve. Cognitive dysfunction and fatigue are among the most common long-term symptoms reported by COVID-19 survivors. These symptoms significantly impact patients' daily lives and are associated with neuroinflammation, neurocognitive impairments, and disruptions in neural pathways. Management strategies for cognitive dysfunction and fatigue in COVID-19 survivors are still being explored. Some potential therapies include Ginkgo Biloba, antiretroviral medications like Nirmatrelvir/Ritonavir (Paxlovid), hyperbaric oxygen therapy (HBOT), manual lymphatic drainage, and transcranial magnetic stimulation (TMS). Physical therapy tailored to individual

capabilities has also has also shown to be quite promising in improving symptoms and quality of life. Longitudinal studies have revealed that while some COVID-19-related symptoms may improve over time, cognitive impairment and fatigue can persist for months or even years post-infection. Cognitive symptoms such as concentration difficulty and cognitive dysfunction are reported by a significant portion of survivors even after 12 months, highlighting the need for continued research and support for affected individuals.

In conclusion, COVID-19 has long-lasting implications for cognitive function and physical capability, with cognitive dysfunction and fatigue being prominent and enduring symptoms in many survivors. Understanding the underlying mechanisms and exploring effective management strategies are essential for improving outcomes and quality of life for those affected by Post-COVID-19.

3. Keywords

SARS-CoV-2, post-COVID-19 condition, COVID Fog, post-acute COVID-19 syndrome, long-haul COVID, long COVID, Rehabilitation in Covid Survivors, COVID-19 infection, Cognitive Dysfunction after COVID-19 infection, Fatigue after COVID-19 infection

4. Introduction

´Following an outbreak of a novel Coronavirus (COVID-19) in Wuhan City, Hubei Province of China, rapid community, regional and international spread has occurred with exponential growth in cases and deaths. On 30 January 2020, the Director-General of WHO declared the COVID-19 outbreak a public health emergency of international concern (PHEIC) under the International Health Regulations (IHR) (2005)´[1]. In the year 2024, through the overall immunization of the world wide population (around 70% of the world population is vaccinated) [2] the importance of Covid-19 in public discourse has diminished. However even today, many patients suffer greatly after a covid-19 infection and are still severely physically impaired for up to 20 months afterwards, as a study conducted by the Charite Hospital in Berlin has found. Furthermore, as per this research, prior to the pandemic, the prevalence of chronic fatigue syndrome globally was roughly 0.3 percent. It is believed by experts that the population affected by this condition has notably increased due to the impact of the COVID-19 pandemic [3]. Acute symptoms of the infections, include dyspnea, fever, myalgia and fatigue. Current studies show that around 10-15% of people infected with SARS-CoV-2 may go on to develop symptoms that can be diagnosed with a post-COVID-19 condition. More than 200 different symptoms have been reported in the context of post-COVID. These symptoms often negatively affect the

quality of life of the survivors [4]. This work will put the focus on the symptoms of fatigue and cognitive dysfunction. The goal of this paper is to cover the pathogenesis of cognitive dysfunction and fatigue in covid condition, the main clinical aspects of cognitive dysfunction and fatigue, the possible managment strategies, and the prognosis for the affected covid survivors.

5. Literature Search Strategy

Literature search was performed from June 1 2023, to March 1 2024, with the already mentioned keywords using PubMed. Only original research articles written in English were selected. Both clinical and preclinical studies were included. Full texts of the relevant articles were extracted after being screened for titles and abstracts. Over 200 Articles were found and over 100 were thoroughly analysed. Inclusion criteria was articles in Englisch Language, COVID-19/SARS-COV-2 affected patients suffering from cognitive dysfunction or fatigue. Exclusion criteria was no Full articles available and children (<18years of age).

6. Definitions

There will be a few terms frequently used in this review. The following paragraph will link these terms to a specific definition relevant for this paper in order to avoid potential confusion. Fatigue or Chronic fatigue syndrome, also known as myalgic encephalomyelitis, is defined by the WHO as a disease that: ´may include chronic, profound, disabling, and unexplained fatigue with coinciding symptoms such as sleep problems or post-exertional malaise`[5]. As seen by this statement, fatigue is a hard to grasp concept with no clear definition, therefore a definitve diagnosis is hard to make. Additionally the Charite states that this type of discomfort might not manifest until several hours or even a day later, persisting typically until the following day or, in numerous instances, for several days or even beyond. It is linked with bodily weakness and commonly accompanied by headaches or muscle pains, often encompassing symptoms related to neurocognitive, autonomous, and immunological functions. This aspect makes it hard to link the symptoms to the causative aspect of a disease or condition [3]. Another term that is important for this paper is cognitive dysfunction. To understand the term cognitive dysfunction, first of all we must understand what normal cognitive function includes. These categories: attention, processing speed, memory, executive function, language and visual-spatial processing, are very important parts of the normal cognitive function and an impairment in one of these will subsequently lead to a cognitive dysfunction [6]. Lastly the focus will be put on the timeline of the Covid-19 infection that can

be divided into three main categories that will be used in this paper, these include: acute, subacute or ongoing symptomatic Covid-19 and post covid. Acute COVID-19 refers to the signs and symptoms experienced for a period of up to 4 weeks. These symptoms are ranging from mild symptoms to severe illness. Possible symptoms include: fever, cough, dyspnoe, fatigue, muscle or body aches, headache, anosmia, ageusia and many more [7]. Ongoing symptomatic COVID-19 or subacute infection entails signs and symptoms persisting from 4 weeks up to 12 weeks. The symptoms can be a mix of both acute and Post-Covid-19 symptoms. Post-COVID-19 syndrome refers to signs and symptoms emerging during or after a COVID-19 infection, lasting more than 12 weeks, without explanation by another diagnosis. It typically presents with clusters of symptoms, often overlapping, that may fluctuate and affect various bodily systems [8-9]. The most common symptoms observed in post-acute COVID-19 and the timeline of COVID-19 infection are summarized in this Figure 1 [10]:

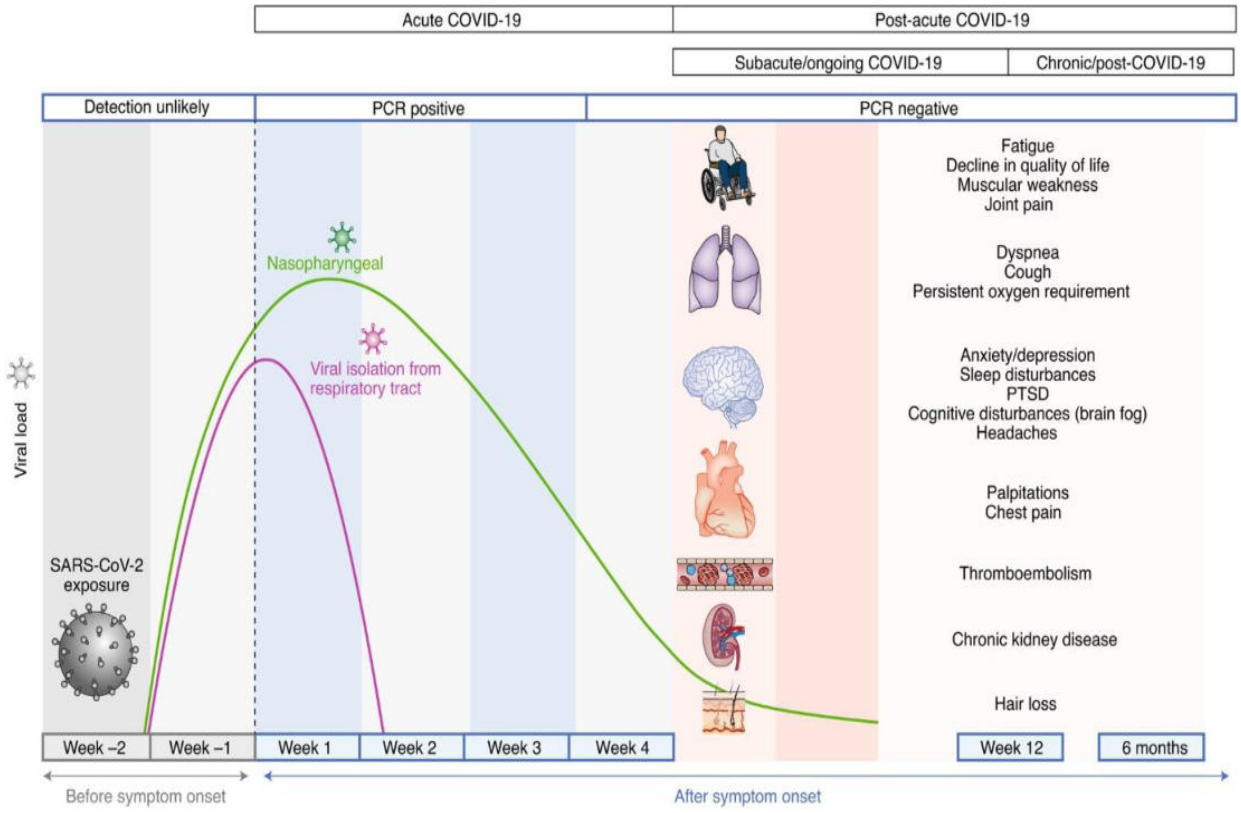

Figure 1: [10] Timeline of COVID-19 Infection

7. Pathogenesis of Cognitive Dysfunction and Fatigue in COVID Condition

The exact source of neurological symptoms in COVID-19 remains partially elusive, though numerous theories are currently under investigation. Several potential mechanisms of nervous system dysfunction and damage during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are being explored. These include direct invasion and harm inflicted on the nervous system by the virus itself, autoimmune reactions targeting the nervous system during infection, endothelial dysfunction coupled with coagulation problems, and the adverse impacts of severe systemic COVID-19 on neurological functions.

7.1 Direct Viral Neurological Invasion

A significant indication that SARS-CoV-2 might penetrate the central nervous system (CNS) would be finding the virus in cerebrospinal fluid (CSF). Yet, the majority of patients displaying neurological symptoms and confirmed SARS-CoV-2 infection did not show evidence of the virus in their cerebrospinal fluid (CSF) when tested using RT-PCR [11]. This still does not give us a definitite result about this potential mechanism of entry into the CNS.

Recent studies [12-13] indicate that ACE2 serves as a crucial entry receptor for SARS-CoV-2, facilitating its infection of various host organs. While previous reports have documented SARS-CoV-2 infection in the brain, the presence of ACE2 throughout the brain remains uncertain. Investigations have revealed relatively high ACE2 expression in specific human brain regions, particularly in many neurons within the middle temporal gyrus and posterior cingulate cortex. Conversely, ACE2 expression was negligible in the human prefrontal cortex (PFC) and minimal in the hippocampus. Additionally, ACE2 expression in the mouse brain mirrored that of humans, with notable presence in the olfactory bulb and limited expression in pericytes and endothelial cells. These findings outline the distribution of ACE2 in human and mouse brains, supporting the notion that SARS-CoV-2 can potentially infect the brain and induce CNS symptoms in COVID-19 patients. As another study has shown [14] that olfactory epithelial cells express high levels of ACE2, meaning that the olfactory nerve could be a possible entry route into the CNS for the virus. This could also be supported by the common symptom of anosmia experienced by many COVID patients. According to Fotuhi et al. [15] the potential cellular mechanism of action of SARS-CoV-2 could be seen in this Figure 2:

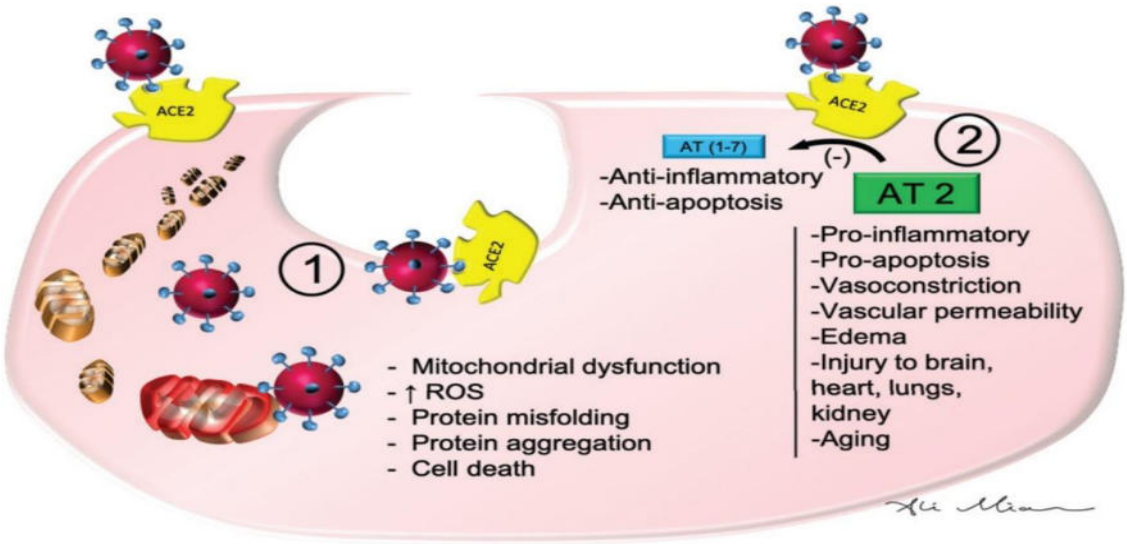

Figure 2: [15] Cellular mechanism of action of SARS-CoV-2

The process involves the attachment of the virus to ACE2 receptors, enabling its entry into epithelial cells lining blood vessels and various organs. Subsequently, once inside the cell, the virus can cause damage to mitochondria and lysosomes, leading to increased levels of reactive oxygen species (ROS), protein misfolding, aggregation, and eventual cell death. Moreover, the virus, by binding to ACE2, inhibits the metabolic conversion of Angiotensin 2 (AT2) to AT (1-7). This results in heightened levels of AT2, which are associated with heightened inflammation, vasoconstriction, increased vascular permeability, edema, and vascular damage in organs such as the lungs, brain, heart, and kidneys. These processes also contribute to pro-apoptotic mechanisms and accelerate aging processes. The interaction between SARS-CoV-2 and ACE2 is a crucial step in the development of clinical symptoms in COVID-19 patients. ACE2 plays a vital role in regulating blood pressure by modulating the angiotensin-renin-aldosterone pathways. Its function includes facilitating the conversion of angiotensin II to angiotensin (1–7). Elevated levels of angiotensin II are associated with conditions such as vasoconstriction, kidney dysfunction, heart ailments, apoptosis, and oxidative processes that promote aging and contribute to brain degeneration [15]. Interestingly, Swank et al. [16] found elevated levels of Spike protein circulating in patients diagnosed with post-COVID-19 for several months following SARS-CoV-2 infection, whereas individuals without long-term complications did not exhibit this phenomenon. The study assessed the levels of SARS-CoV-2 antigens and cytokines in plasma samples obtained from patients with post-acute sequelae of SARS-CoV-2 and those with COVID-19. Notably, the presence of circulating SARS-CoV-2 spike protein in the majority of Post-Covid patients was observed. Despite the limited sample size, the detection of spike protein at various time intervals spanning 2 to 12 months post-infection is a significant discovery. The temporal variability in antigen levels among some

individuals underscores the importance of collecting samples longitudinally. Additionally, only a minority of the post-COVID cohort required hospitalization, indicating that the findings primarily pertain to SARS-CoV-2 infection rather than consequences of severe illness and hospital care [16]. Another study by Fontes-Dantas et al. [17] supports this theory, as the researchers showed that administering Spike protein directly into the brains of mice had a delayed effect on cognitive function, mimicking the symptoms seen in post-COVID-19 syndrome. They also revealed that neuroinflammation and an increase in microglia in the hippocampus are responsible for the memory impairment induced by Spike protein, achieved through the complement-dependent removal of synapses [17].

7.2 Immune Dysregulation

Another potential mechanism could involve the elevated levels of cytokines, coupled with hypoxia, that might trigger neuroinflammation by affecting blood and CSF barriers, potentially resulting in vascular damage within the CNS. Additionally, the expression of cytokines by neural cells could contribute to neurocognitive issues or worsen neuropsychiatric symptoms in patients with existing conditions, potentially impacting hippocampal neurogenesis, neuronal circuitry, or mitochondrial function [18-19]. This mechanism could also be supported by Phetsouphanh et al. [20] work who discovered that individuals experiencing post-COVID displayed heightened activation of innate immune cells, depletion of naive T and B cells, and sustained elevation in the expression of both type I interferon (IFN-β) and type III interferon (IFN-λ1), which could persist for up to 8 months post-infection [20]. Another study conducted by Fernández-Castañeda et al. found [21] that after mild respiratory COVID in mice, there were observable long-term effects on hippocampal neurogenesis, oligodendrocytes, and myelin, along with increased levels of certain cytokines/chemokines like CC-chemokine ligand 11 (CCL11) in the cerebrospinal fluid. Administering CCL11 systemically led to microglial reactivity in the hippocampus and impaired neurogenesis. Similarly, humans experiencing cognitive symptoms post-COVID had higher levels of CCL11. When compared to SARS-CoV-2, mild respiratory influenza in mice produced similar effects on microglial reactivity, oligodendrocyte loss, impaired neurogenesis, and elevated CCL11 initially. However, after influenza, only elevated CCL11 levels and hippocampal issues persisted. These findings suggest parallels in neuropathophysiology between cancer therapy and respiratory SARS-CoV-2 infection, potentially contributing to cognitive issues even after mild COVID [21].

7.3 Endothelial Dysfunction and Coagulopathy

Abnormalities in blood clotting are well-documented in COVID-19, with thrombotic complications occurring frequently in various organs, particularly in severe cases. Elevated levels of D-dimer, indicating microangiopathic changes, are commonly used as a significant prognostic biomarker [22]. Furtheremore Pathological examination has revealed endothelial dysfunction within the CNS of COVID-19 patients, presenting as endotheliitis. This condition is characterized by microbleeds, petechial hemorrhages along blood vessel walls, and infiltration of T cells and macrophages around blood vessels. These changes could explain the neurological symptoms persisting after a COVID-19 infection [23].

7.4 Severe Systemic COVID-19 Disease

The adverse impacts of severe systemic COVID-19 on the nervous system can be seen by the research conducted by Frontera et al. [24] which revealed that approximately one out of every eight COVID-19 hospitalized patients developed Toxic Metabolic Encephalopathy (TME), independent of sedative medications' effects. TME was notably linked to a 24% higher risk of in-hospital mortality. Additionally, patients with TME experienced prolonged hospitalization and were less likely to be discharged home.The aforementioned findings prompt an important inquiry into whether and to what degree these neurological symptoms stem from SARS-CoV-2 infection as opposed to being typical complications of critical illness.

7.5 Potential Affected Brain Regions

Hugon et al. [25] have found out that hypometabolic regions in the anterior and posterior cingulate cortex were present after a covid infection. Prior research [26], both experimental and clinical, has indicated that the anterior and posterior cingulate cortex play roles in regulating emotions, memory processes, depressive states, and decision-making. Specifically, the anterior cingulate cortex receives inputs related to reward outcomes from the orbitofrontal cortex, while the posterior cingulate cortex influences connections with the hippocampus. Dysfunction in these neural pathways could account for the cognitive symptoms observed in affected individuals, which manifest as difficulties in episodic memory, as well as abnormalities in executive and attentional functions.

8. Clinical Aspects of Cognitive Function and Physical Capability During and After Covid

The acute phase of COVID-19 typically resolves completely within 2–4 weeks after infection. However, a significant portion of individuals continue to experience symptoms for 1–6 months

post-infection or even longer for various reasons. This diverse group of patients is often diagnosed with “long COVID“ or “post COVID“ Those who fail to recover within 6 months, lack a medical explanation for their persistent symptoms, and exhibit fatigue, cognitive difficulties ("brain fog"), disrupted sleep, and psychiatric symptoms. They may receive a diagnosis of Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Due to the early stage of recovery for many COVID-19 patients and the limited available data, it remains unclear what proportion of individuals with post-COVID will develop ME/CFS over time [27].

ME/CFS is a complex and frequently enduring condition that affects multiple bodily systems, resulting in significant morbidity and profoundly impacting patients' health and quality of life. It is estimated that between 836,000 and 2.5 million individuals in the United States are affected. Those with ME/CFS often find themselves incapable of engaging in their usual daily activities, with up to a quarter being confined to their homes or bed for extended durations. Consequently, the personal and societal consequences of this illness are immense [28].

The clinical aspects of cognitive funtion and physical capability during and after covid are very similar. The main difference is that in the acute phase, the symptoms can be explained by the acute infection with the COVID-19 virus that leads to the aforementioned symptoms. These symptoms can appear in many other infectious diseases and do not make COVID-19 unique. However as already previously mentioned in this paper, it is not so easy to explain why the symptoms do not disappear after the initial phase of the infection. In Figure 3 the differences in symptoms and their distribution between acute and post-COVID are summarized [29]:

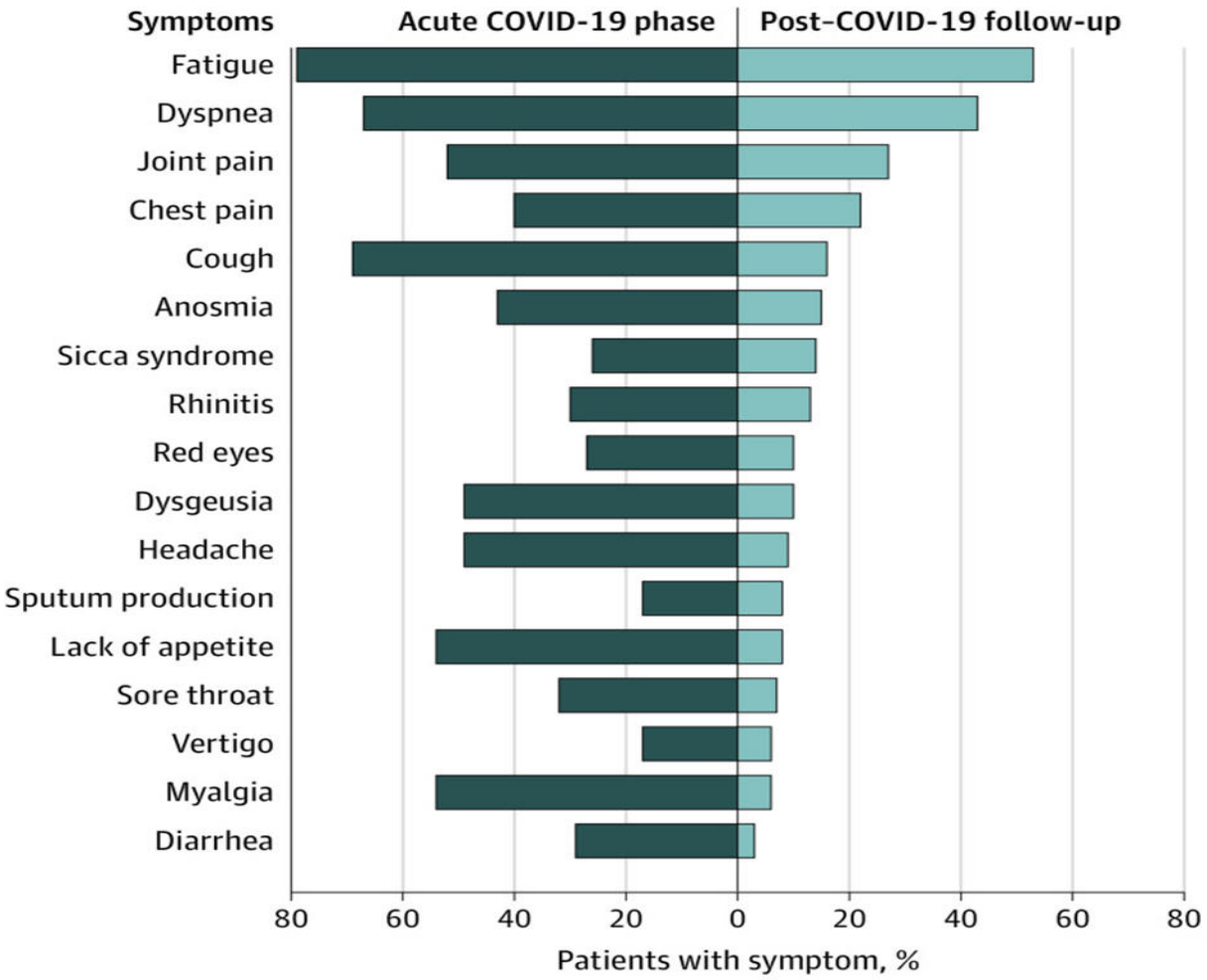

Figure 3: [29] Acute and Post COVID-19–Related Symptoms

Researchers from Italy examined 143 individuals who had tested positive for COVID-19 once their most severe symptoms had subsided. After 60 days from the onset of their illness, over fifty percent of the patients still experienced several troublesome symptoms with fatigue being the most common, with 41% reporting a decline in their quality of life. This study and others show that in the acute phase almost 80% reported fatigue and this number (53.1%) was still high in the post covid-19 folow up. This makes fatigue one of the the most common and relevant remaining symptoms in Post covid [29].

Hugon et al. [25] have described the symptoms in their studies as follows: After returining home patients gradually developed cognitive disorders, including combining memory problems, slowness of ideation, general fatigue, anxiety, and depression. Even walking and memory problems as well as speech deficits occurred. This shows that the symptoms can be very variable and affect each individual differently [25]. According to another study [30], there was a notable increase in patients reporting considerable levels of executive dysfunction. The most common neuropsychological impairments observed were in long-term memory (28.7%),

executive functioning (24.2%), and attention. Apathy emerged as the most influential predictor of fatigue when compared to both physical and psychosocial fatigue components in the models. In terms of the physical component, deficits in executive control (specifically switching abilities) and anxiety also emerged as robust and significant predictors. The study highlighted executive functioning and attention as key cognitive factors associated with fatigue [30].

These findings are further supported by Helms et al. [11] who stated that, 15 out of 45 of their discharged patients (33%) displayed symptoms of a dysexecutive syndrome, characterized by inattention, disorientation, or poorly coordinated movements in response to commands. Also highlighting the impaired physical capability of COVID patients. In another study conducted by Carbone et al. [31] the cognitive function in COVID-19 patients was assessed using eye tracking 12 months after disease onset. It was found that patients made significantly more directional errors and more anticipatory errors in the tasks compared to healthy controls. Furthermore, those patients requiring hospitalization performed worse than healthy controls and patients who were managed as outpatients. These results show that the cognitive functions are impaired in patients even 1 year after a COVID-19 infection [31].

Other studies [32] also demonstrate the prominent occurrence of cognitive impairment in over half (63%) of patients, along with decreased scores in usual activities and self-care, which underscores the potential limitation of societal engagement for individuals with post-COVID conditions. Employment was similarly affected in the majority of patients, though it is not clear whether this stemmed directly from COVID-19-related disability or from broader pandemic-related impacts on workplace operations. Self-reported levels of physical activity notably decreased, possibly aligned with the likelihood of symptom exacerbation. This impact on physical function [32] can be demonstrated in figure 4:

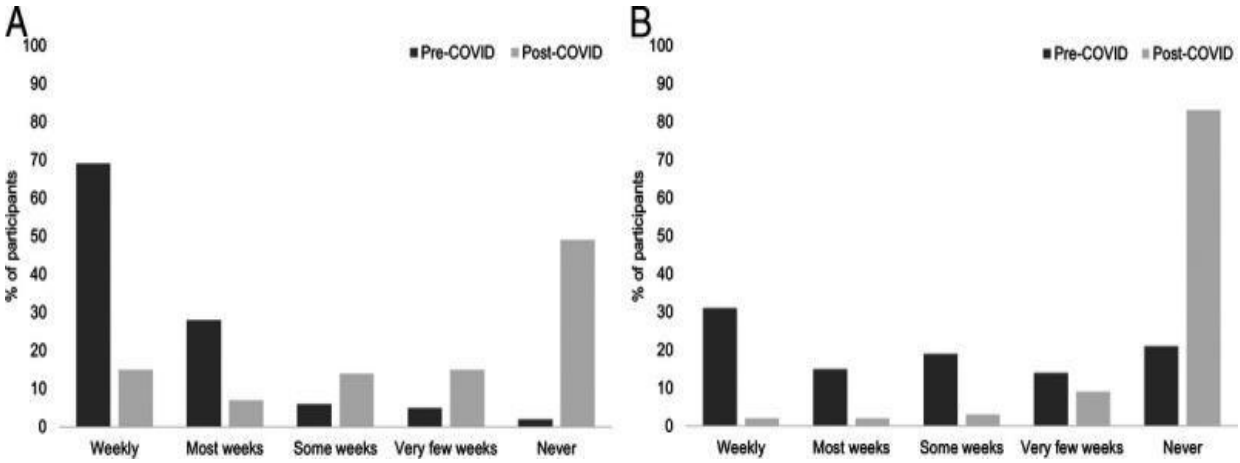

Figure 4: [32] Levels of moderate (A) and vigorous (B) intensity physical activity regularly completed (150 mins/wk) before and after COVID-19 infection in all patients (N = 156)

It can be clearly seen that the frequency of vigorous and even moderate physical activity regularly completed has drastically decreased, comparing the Pre- and Post-COVID results. Saucier et al. [33] conducted a study that uncovered deficiencies in various cognitive functions through neurocognitive assessment. A deficit in cognitive flexibility and inhibition was observed in 38.8% of patients, identified by abnormal results from the Hayling and Brixton tests (tests for clinical assessments of executive functioning), Overall, 58.2% of participants exhibited abnormal results on at least one neurocognitive scale. Mild impairment was observed in 39.6% of the sample, moderate impairment in 17.2%, and moderately severe impairment in 1.5%. None of the participants showed severe cognitive impairment. As the study highlighted an inhibition deficit in 38.8% of post-acute COVID-19 patients, this indicates difficulties in inhibiting automatic verbal responses and resisting distraction interference, which are further signs of cognitive impairment [34].

Very similar results were found in a study performed by Delgado-Alonso et. al. [35] in which they concluded that that COVID-19 patients experiencing cognitive symptoms demonstrated decreased cognitive abilities, particularly in attention-concentration and executive functioning, episodic memory, and visuospatial processing. Cognitive performance showed some correlation with olfactory dysfunction and sleep quality, albeit to a lesser degree, but not with anxiety or depression. The various studies underscore the profound and enduring impact of COVID-19 on cognitive function and physical capability, affecting numerous bodily systems and significantly diminishing patients' health and quality of life. Post-COVID-19 patients exhibit persistent symptoms resembling ME/CFS, particularly cognitive dysfunction and fatigue. Research indicates that fatigue remains a prevalent and troublesome symptom even after the acute phase of COVID-19, affecting over half of patients in follow-up studies. Cognitive impairments vary widely among individuals, encompassing memory problems, slowness of ideation, executive dysfunction, visuospatial processing, attention deficits and many more. These cognitive issues can persist even a year post-infection. Moreover, societal engagement and employment are significantly impacted by these post-COVID conditions, emphasizing the need for further research and support for affected individuals.

9. Management Strategies and Rehabilitation to Improve Cognitive Function and Fatigue in Covid

At present, there is no one-size-fits-all medication or therapy that effectively addresses cognitive dysfunction or fatigue in individuals who have survived COVID-19. Nonetheless, numerous studies have been conducted to explore potential treatment options that may offer

benefits in managing these symptoms. There are still many studies that are taking place, or potential therapeutic agents were studies are planned, [36-38] that could identify new potential therapies that could help against the post-covid syndromes of fatigue and cognitive impairment. In the following part, a few promissing potential therapeutic options will be explored.

9.1 Ginkgo Biloba

Ginkgo, known scientifically as Ginkgo biloba (standardized extract EGb761®), is among the ancient tree species still in existence today. Extracts derived from its distinctive fan-shaped leaves are commonly used in most ginkgo products. The beneficial properties of ginkgo are primarily attributed to flavonoids, known for their potent antioxidant properties, their antiinflammatory effects and terpenoids, which aid in enhancing circulation by causing cerebral vasodilatation and reducing platelet aggregation [39-40].

In a research conducted by Zifko et al. [41], patients experiencing post-COVID symptoms were administered a daily dose of 2×80 mg of EGb 761. No adverse effects were observed, and significant improvements or full recovery of cognitive deficits, along with other symptoms like fatigue and hyposmia, were noted within a monitoring period of up to 6 months. These findings suggest that EGb 761 could be a potentially safe treatment option for post-COVID-19 patients experiencing cognitive symptoms [41].

9.2 Nirmatrelvir/ Ritonavir (Paxlovid)

Nirmatrelvir is an antiretroviral medication that inhibits the 3C-like protease (3CL PRO) and is taken orally. It is typically administered alongside ritonavir, another antiretroviral protease inhibitor. The combination of both is known as Paxlovid [42]. Preiss et al. [43] performed a study to find out whether paxlovid treatment during acute covid-19 had an impact on post-covid onset. They found that Paxlovid had a significant protective effect against the onset of novel cognitive and fatigue symptoms in the post-acute period. As can be seen in figure 5:

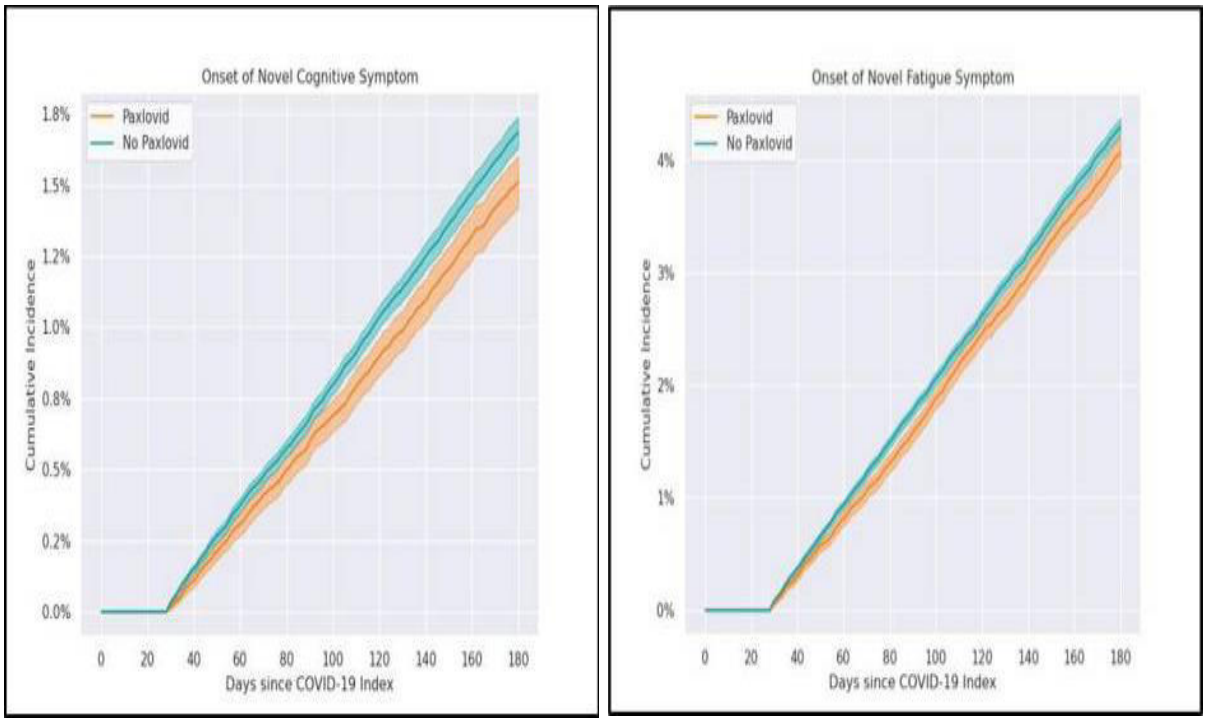

Figure 5: [43] Cumulative incidence of novel Cognitive and Fatigue Symptoms in Paxlovid treated vs. Non-Paxlovid-Treated patients by outcome measure; between 29–180 days

Similar results were found in another study performed by Xie et al. [44]. This study, conducted on a cohort of individuals with SARS-CoV-2 infection and at least one risk factor for severe disease progression, revealed that administering nirmatrelvir within 5 days of a positive test result was linked to a decreased risk of post-acute COVID complications across various risk levels within the cohort. The collective evidence suggests that early treatment with nirmatrelvir during the acute phase of COVID-19 could lower the likelihood of post-acute adverse health outcomes. Compared to the control group, individuals receiving nirmatrelvir, regardless of vaccination status or history of infection, experienced reduced risk of post-COVID symptoms such as fatigue, malaise, muscle pain, and neurocognitive impairment [44].

9.3 Hyperbaric Oxygen Therapy (HBOT)

A few studies have covered the potential benefits of Hyperbaric oxygen therapy (HBOT). Their findings suggest that HBOT has the potential to promote neuroplasticity and ameliorate various symptoms. In a study conducted by Zilbermann-Itskovich et al. that measured several symptom categories in follow-up assessments that were performed at baseline and 1-3 weeks after the last treatment session. Cognitive, psychiatric, fatigue, sleep disturbances as well as pain, in individuals with post-COVID-19 syndrome were signifcantly better. The positive impact of HBOT may be linked to enhanced brain perfusion and neuroplasticity in areas associated with cognitive and emotional functions [45]. Based on the aforementioned study a longitudinal follow-up study was performed by Hadanny et al. [46]. The research assessed the lasting effects

of HBOT on the post-COVID syndrome over a one-year period. This extensive longitudinal follow-up involved 31 patients experiencing cognitive symptoms after COVID-19, all of whom received 40 daily HBOT sessions. In this extended longitudinal monitoring of the group receiving active treatment from the initial randomized controlled trial, it was observed that the positive effects of HBOT on the quality of life, emotional well-being, sleep quality, and neuropsychological symptoms (cognitive impairment, fatigue) of post-COVID patients persisted for over a year after the final HBOT session. Across all domains of quality of life, emotional factors, sleep quality, and pain severity and interference, the long-term outcomes did not significantly differ from the beneficial effects observed 1–3 weeks following HBOT [46]. These findings are supported by other studies [47-49] showing improvements in cognition, physical functioning and fatigue after the treatment with HBOT.

9.4 Manual Lymphatic Drainage

Overall et al. [50] conducted two case reports wherein two patients experiencing post-COVID symptoms, including fatigue, underwent six 45-minute sessions of Manual Lymphatic Drainage (MLD) weekly, followed by a review and treatment after three months. In both cases, improvements were observed after the third treatment, with further enhancement noted at the three-month follow-up. Before the intervention, both patients scored high (≥4) on the Revised Piper Fatigue Scale, indicating the need for professional intervention. Following the MLD treatment course, neither patient reached this threshold, which aligns with findings by Heald et al. [51] showing an average 50% reduction in fatigue-related states after approximately nine sessions using the Perrin method with self-massage and home exercises. These findings suggest that MLD may provide a non-invasive, non-pharmaceutical and low-risk approach to alleviating post-COVID symptoms such as fatigue [50].

9.5 Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) functions based on the principles of electromagnetic induction. In essence, when an electric current passes through a coil, it creates a magnetic field through electromagnetic induction. This magnetic field then transfers to another coil, which is in close proximity to neural tissue, leading to the induction of a secondary electrical field that stimulates the tissue. Neurons have axonal processes that are curved or bent, intersecting with the lines of force of the magnetic field at right angles. These processes act similarly to secondary coils, thus experiencing electrical effects. By changing the direction of current flow at high frequencies, rapidly alternating magnetic fields can be generated, which stimulate the neurons and their fibers underneath. This method of stimulation, delivered in pulses, is termed pulsed

Electromagnetic Field (EMF) stimulation, resulting in continuous depolarization. Such pulsed stimulations are acknowledged for their ability to correct impaired cell function and promote healing. Repetitive TMS operates on comparable principles and yields observable clinical effects [52]. The effectiveness and safety of this therapeutic modality is demonstreated by the fact that it is already in use for resistant depression [53].

In a Japanese study [54] 23 patients suffering from post-COVID, presenting with predominant neuropsychiatric symptoms of chronic fatigue (n = 12) and cognitive dysfunction (n = 11), underwent TMS treatment. Comparing the pre and post TMS assessment scores for fatigue and cognitive dysfunction, significant improvements could be observed. The Performance Status score, assessing fatigue severity, showed improvement from 5.4 to 4.2, while the score on the Perceived Deficits Questionnaire–Depression 5-item, indicative of cognitive function, improved from 10.0 to 6.3. Although some patients reported pain at the stimulation site during TMS as a side effect, no serious adverse events were observed [54]. A very similar study conducted by Sasaki et al. [55] who among other things compared the pre and post TMS results of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV), which is a frequently utilized set of tests for evaluating intellectual and cognitive capacities [56].

Table 1 demonstrates the alterations in WAIS4 components from the pre to post rTMS evaluations. All IQ components of WAIS4 (VCI, PRI, WMI, PSI, and FSIQ) exhibited significant enhancements at the post-assessment (all $P < 0.05$).

Table 1:

	Pre	Post	P value
FSIQ	94.6 (10.9)	104.4 (13.0)	< 0.05
VCI	93.5 (9.0)	100.5 (10.0)	< 0.05
PRI	95.4 (11.5)	106.4 (10.3)	< 0.05
WMI	97.9 (17.5)	105.5 (19.5)	< 0.05
PSI	95.4 (11.5)	106.4 (10.3)	< 0.05

Table 1: [55] Changes in Iqs of WAIS4 before rTMS and after ten sessions of rTMS

These findings are very significant and correlate to the previously mentioned study carried out by Noda et al. [54]. Furthermore, the Brief Fatigue Inventory (BFI) was assessed, registering a value of 5.7 ± 2.3 before the intervention, which notably declined to 1.9 ± 1.8 after the intervention. This outcome underscores the therapeutic impact of TMS on fatigue. The afforementioned studies [54-55] underscore TMS as a promising, effective and safe option for treating post-COVID symptoms such as fatigue and cognitive dysfunction.

9.6 Physical Therapy

Physical therapy could be a potential way of relieving the symptom of fatigue. However before suggesting physical activity, such as exercise or sports, as part of rehabilitation for individuals with post-COVID, it's essential to screen them for worsening symptoms after exertion. This involves closely observing signs and symptoms during and after increased physical activity and continuously monitoring their response to any physical interventions. The pace and intensity of the exercises should be adjusted according to the individual needs of the patients [57]. As the study conducted by Tabacof et al. [32] found that physical exertion was the most common cause of symptom exacerbation.

The primary outcome of another study [58] revealed that an 8-week supervised exercise regimen, customized to each participant and incorporating multicomponent training, substantially enhanced health indicators such as quality of life, fatigue, and muscular strength. The individualized treatment approach, which included adjusting the intensity of training within each session while ensuring completion of the prescribed volume, prevented any patients from discontinuing due to tolerance issues.

Another study [59] assessed pre-post impact on physical performance of multi-component therapeutic exercise for post-COVID-19 rehabilitation in a post-acute care facility. Following the intervention (with an average duration of 8.2 ± 1.7 days), there was a statistically significant enhancement in all physical performance metrics when comparing the initial and final values across the entire sample. In summary the findings about physcial exercise to treat COVID-19 related fatigue show that it can significantly improve the patients general wellbeing, however it has to be performed according to the patients capabilities in order to prevent post-exertional malaise.

10. Changes in Cognitive Function and Physical Capability (Fatigue) in Covid Survivors Over Time

Overall, COVID-19-related persistent symptoms tend to ameliorate with time; [60] nevertheless, neurological symptoms may endure longer compared to other manifestations. Concentration difficulty emerged as the most prevalent symptom persisting for up to 12 months, affecting 22.4% of respondents, followed by cognitive dysfunction at 21.2%, with fatigue also being notable, affecting 16.2% of respondents [61]. As can be seen in Figure 6:

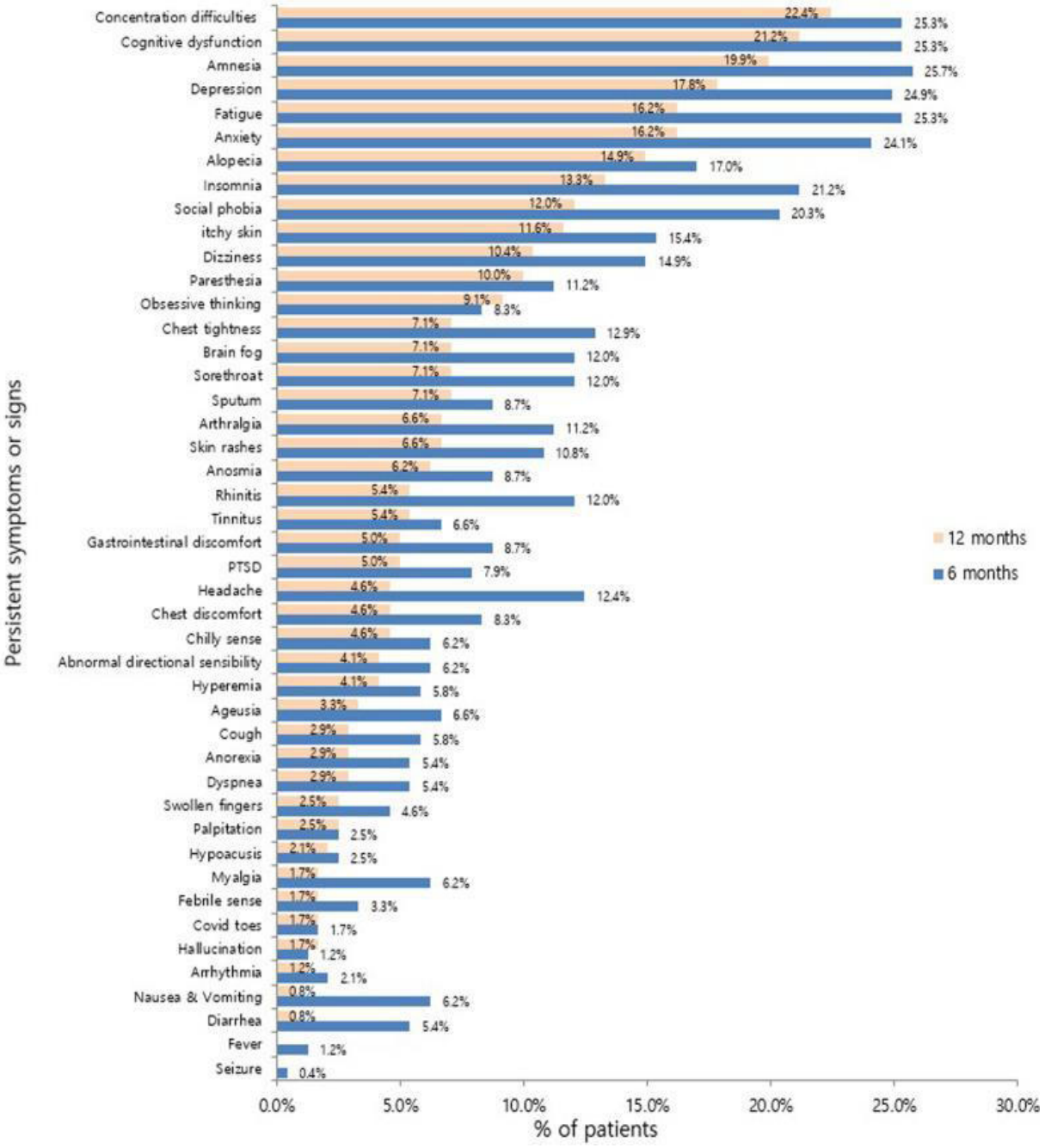

Figure 6: [61] Distribution of 45 persistent symptoms or signs over 12 months after acute COVID-19 infection

Huang et al. [62] perforemed a 6-month cohort study to explore the long term consequences of COVID-19. It was found that fatigue or muscle weakness (63%) was the most common symptoms making it an even more relevant symptom of post-COVID.

Saucier et al. [33] conducted a large exploratory study and followed patients with post-COVID over a 16-month time period. They compared the cognitive impairments of the patients in that timeframe. In Figure 7 it is illustrated how the prevalence of abnormal scores in the four cognitive tests across each of the four subgroups changed over time. Over the study period, the prevalence of abnormal scores decreased in three of the four tests, reaching zero in the last 4 months for Oral Trail Making Test A and B (O-TMT-B, O-TMT-A), and Modified Telephone

Interview of Cognitive Impairment (TICS-m). However, abnormal scores for Hayling and Brixton tasks remained consistently high, with a prevalence of 50% persisting even up to 16 months post-infection [33].

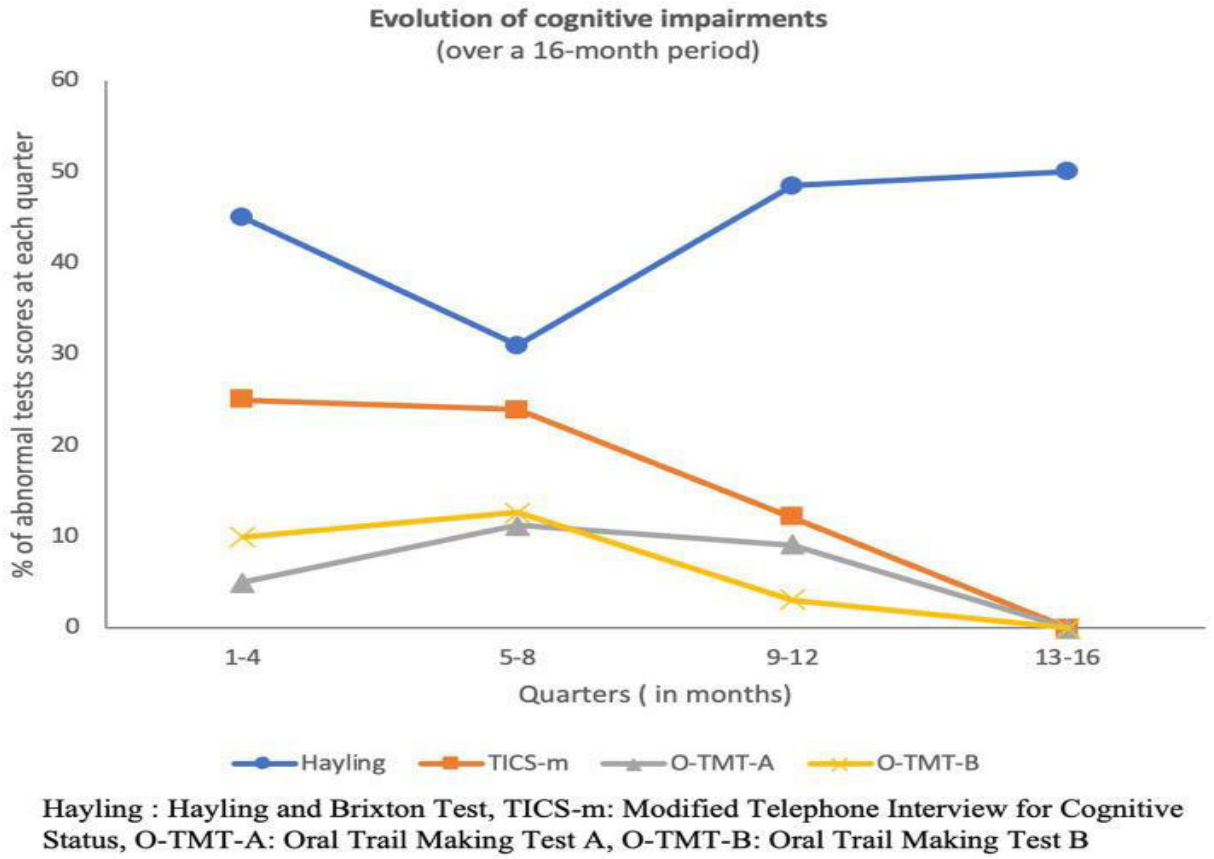

Figure 7: [33] Cross-sectional evolution of cognitive impairments throughout the study period

The occurrence of impaired cognitive efficiency decreased to 0% after 16 months following the infection. Conversely, the prevalence of deficits in cognitive inhibition remained consistently high from 1 to 16 months post-infection (Hayling and Brixton tasks). The pattern of mild impairment differed between the early and late assessment groups, with almost all patients showing mild impairment after 6 months also demonstrating an inhibition deficit. These findings indicate that individuals with moderate impairment following COVID-19 infection may experience persistent deficits, whereas those with mild cognitive impairment might witness most of their deficits resolving within the initial 6 months post-infection, except for cognitive inhibition [33]. In another research conducted by Rafi Hadad et al. [63] it was observed that cognitive symptoms endured for over 10 months among 14 out of 19 (93%) participants who returned for follow-up. In certain instances, these symptoms persisted for more

than a year. This number can be explained by a small sample size, however even taking that into account, it still shows the long-term cognitive consequences of COVID-19.

These observations could be congruent with the previously mentioned study [33] as cognitive symptoms lasted to around 9-12 months and only reached 0% for most tests afer 13-16 months. Similar results were found by Liu et al. [64]. They found that, 12 months after discharge, cognitive impairment was observed in 12.45% of survivors. Those with severe cases exhibited lower Telephone Interview of Cognitive Status scores compared to individuals with non-severe cases and control subjects at the 12-month mark. Severe COVID-19 cases were linked to an elevated risk of early-onset, late-onset, and progressive cognitive decline.

11. Discussion

This thesis underscores the enduring impact of COVID-19 on patients, extending far beyond the initial infection. Months and even years post-infection, individuals continue to grapple with a spectrum of long-term symptoms, with fatigue and cognitive impairment emerging as prevalent and persistent challenges, significantly diminishing their quality of life over extended periods. Nevertheless, amidst these lingering effects, glimmers of hope arise from the burgeoning body of research dedicated to unraveling the post-COVID pathogenesis and exploring potential therapeutic interventions. The precise cause of neurological symptoms in COVID-19 is still not fully understood, but there are several theories being actively researched. These encompass direct invasion and damage caused by the virus to the nervous system, autoimmune responses that target the nervous system during infection, endothelial dysfunction combined with clotting issues, and the negative effects of severe systemic COVID-19 on neurological processes. Most likely the pathogenesis is multifactorial and it will not be possible to link it to a single cause. The more we comprehend the pathogenesis, the simpler it becomes to create customized therapies. However even with the aforementioned difficulties in this landscape, various avenues show promise in alleviating the burdensome symptoms endured by COVID-19 survivors. Herbal remedies such as Ginkgo Biloba and novel antiretroviral medications like Paxlovid exhibit encouraging outcomes in clinical trials. Additionally, traditional approaches like manual lymph drainage and physical therapy offer tangible benefits in managing these lingering symptoms. Furthermore, unconventional yet intriguing methodologies such as Transcranial Magnetic Stimulation and Hyperbaric Oxygen Therapy demonstrate efficacy in ameliorating fatigue and cognitive dysfunction, despite not being immediately apparent choices. Looking ahead, the trajectory of post-COVID symptomatology research appears poised to shed further light on its underlying mechanisms, paving the way for

the introduction of more targeted therapeutic modalities. The imperative for such advancements is underscored by the persistent suffering experienced by many COVID survivors, underscoring the urgency for comprehensive solutions to address the enduring ramifications of the disease.

12. Conclusion

The impact of COVID-19 extends far beyond the acute phase of infection, with many individuals experiencing ongoing symptoms and complications long after recovery, which significantly impact the quality of life and the society as a whole. The long-term consequences of COVID-19 on cognitive function and physical capability are profound and multifaceted, posing significant challenges for individuals, healthcare providers, and society at large. Research indicates that COVID-19-related symptoms tend to ameliorate over time, but neurological symptoms may persist longer than other manifestations. Longitudinal studies have shown that while some cognitive deficits may resolve within the first few months post-infection, others may persist for a year or more. Fatigue and cognitive dysfunction, in particular, remain common and troublesome symptoms, affecting a significant proportion of COVID-19 survivors even months after recovery. As the pathogenesis of the diesease development is still not completely understood, research into the mechanisms underlying these symptoms is essential for supporting the growing number of post-COVID-19 survivors worldwide.

There are a few promising potential therapeutic procedures that are being explored, however as there is still not a one-size-fits-all medication or therapy, concerted efforts are needed to develop effective interventions, support mechanisms, and rehabilitation strategies to mitigate the impact of COVID-19 on survivors' health and well-being. By fostering interdisciplinary collaboration and advancing research in this field, we can strive towards improved outcomes and better quality of life for those affected by the pandemic's enduring legacy.

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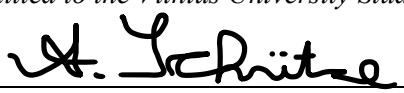
15. Warranty

WARRANTY
of Vilnius University Student Thesis

Name, Surname: Adrian Friederich Schütze
Faculty: Faculty of Medicine
Study programme: Medicine
Thesis topic: Fatigue and Cognitive Dysfunction in COVID-19 Patients: a Narrative Review
Thesis type: Narrative Literature Review
I guarantee that my thesis is prepared in good faith and independently, there is no contribution to this work from other individuals. I have not made any illegal payments related to this work.
Quotes from other sources used in this thesis, directly or indirectly, are indicated in literature references.

I, Adrian Friederich Schütze , confirm (check) [X]

I declare that this thesis is submitted to the Vilnius University Study Information System.

Adrian Friederich, Schütze  08.05.2024
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