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Sleep-related post-COVID sequelae across the COVID-19 pandemic waves in Hungary

Ph.D. thesis

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List of abbreviations

6MWT	6-minute walk test
ACE2	angiotensin-converting enzyme-2
AIS	Athens Insomnia Scale
BMI	body mass index
CTD1	C-terminal domain 1
CTD2	C-terminal domain 2
CO	carbon monoxide
COVID-19	coronavirus disease 2019
CT	computed tomography
E	envelop
EKG	electrocardiography
EQ5D	Health-Related Quality of Life Questionnaire
ESS	Epworth Sleepiness Scale
FEV1	forced expiratory volume in one second
FSS	Fatigue Severity Scale
FVC	forced expiratory vital capacity
ISI	Insomnia Severity Index
JSS	Jenkins sleep scale
KLCO	diffusion coefficient
LDCT	low-dose CT
LSEQ	Leeds Sleep Evaluation Questionnaire
M	membrane
MSLT	multiple sleep latency test
MSQ	Mini Sleep Questionnaire
N	nucleocapsid
NIV	non-invasive ventilation
NTD	N-terminal domain
PEmax	maximal expiratory pressure
PImax	maximal inspiratory pressure
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index

PSQI-HUN	Pittsburgh Sleep Quality Index - Hungarian validated form
R0	basic reproduction number
RBD	receptor-binding domain
RBM	receptor-binding motif
RNA	ribonucleic acid
S protein	spike protein
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
ssRNA	single-stranded RNS
TLC	total lung capacity
TLCO	CO transfer factor
TMPRSS2	type II transmembrane serine protease
VAS	Visual Analogue Scale
WHO	World Health Organization
VOC	variants of concern

1. Introduction

1.1. Coronavirus

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), a member of the coronavirus family (1). The first case of SARS-CoV-2 infection dates back to November of 2019, in the Wuhan province of China, initially referred to as 'pneumonia of unknown origin.' The World Health Organization (WHO) declared the outbreak a pandemic on March 11, 2020 (2). As of June 2023, SARS-CoV-2 had caused more than 768 million confirmed infections and over 6.9 million deaths worldwide (3). The mortality rate is commonly used to characterize the evolving severity of COVID-19 (4). Since the beginning of the pandemic, global mortality rates have decreased, even though subsequent waves of infection have been more transmissible. This phenomenon can be explained by the accumulation of mutations in the SARS-CoV-2 virus and the enhancement of host immune responses, likely due to vaccination or prior infection (5).

Despite the temporal decrease in mortality, hospital mortality for SARS-CoV-2 infection continues to exceed that of influenza (6-9). The underlying factors behind changes in mortality rates are complex and not yet fully explored. This may be attributed to significant improvements in hospital care for COVID-19, reduced hospital overcrowding, as well as factors such as sex, age, comorbidities, previous infections, and vaccination status (10). In addition to epidemiological measures, the development of a coronavirus vaccine has played a crucial role in the fight against the infection. The cornerstone of defense against the infection, beyond classical epidemiological measures, was the creation of a coronavirus vaccine. Currently, several vaccines with different types and mechanisms are available, and demonstrate adequate efficacy (2).

Virus virulence also contributes to disease severity alongside host factors such as immunity and susceptibility, and is defined as the infection-induced increase in morbidity and mortality. However, it does not necessarily decline over time, as models often show a trade-off between transmissibility and virulence (11, 12).

1.1.1. SARS-CoV-2 biology and host interactions

Coronaviruses are known to infect humans through zoonotic transmission from animal hosts. The genetic similarity between SARS-CoV-2 and bat coronaviruses suggests that bats were the primary reservoirs for the zoonotic infection that led to COVID-19 (13). Transmission occurs primarily via respiratory droplets and aerosols produced during coughing, sneezing, or speaking, and is mitigated by physical distancing and improved ventilation (14-16).

Infectiousness refers to the period during which a person can transmit the infection to others. Infectiousness begins during the incubation period (up to 14 days post-exposure), peaking about one day before symptom onset and declining within the first week of symptoms, correlating with high viral RNA loads in respiratory samples. (15-18). Infection risk depends on exposure type and duration, host immunity, age, and comorbidities (16, 18-21). The pandemic spurred rapid vaccine and antiviral development, but ongoing viral evolution challenges their efficacy as virus variants could exhibit enhanced transmissibility, immune escape, or altered virulence (22, 23).

The structure of the SARS-CoV-2 virus is consistent with that of other viruses in the coronavirus family. Coronaviruses are single-stranded RNA (ssRNA) viruses with a lipid envelope. The viral membrane's lipid envelope also contains various proteins molecules with specific properties (1, 24). Concerning the structure of the SARS-CoV-2 virus, it features a spike (S) glycoprotein on its surface in the form of a homotrimer, which binds to the angiotensin-converting enzyme 2 (ACE2) (1) (Fig. 1). In addition, the structural proteins of the virus include the envelope (E) protein, the membrane (M) protein, and the RNA-binding nucleocapsid (N) protein. These proteins are involved in the packaging, assembly, and release of newly formed viral particles from the host cell. The viral S glycoprotein mediates host cell entry by binding ACE2 receptors, with its S1 subunit containing the receptor-binding domain (RBD) and N-terminal domain (NTD), key targets for neutralizing antibodies and mutation sites facilitating immune evasion. Proteolytic activation of S protein by the type II transmembrane serine protease (TMPRSS2) or endosomal cathepsins exposes fusion peptides, enabling membrane fusion and viral entry. SARS-CoV-2 manipulates host membranes to form replication organelles and employs multiple immune evasion strategies, including suppression of antigen presentation and host protein synthesis. RNA recombination between co-

infecting coronaviruses contributes to viral diversity and evolution, with selection favoring enhanced replication, transmission, and immune escape (1, 3, 23, 25-42).

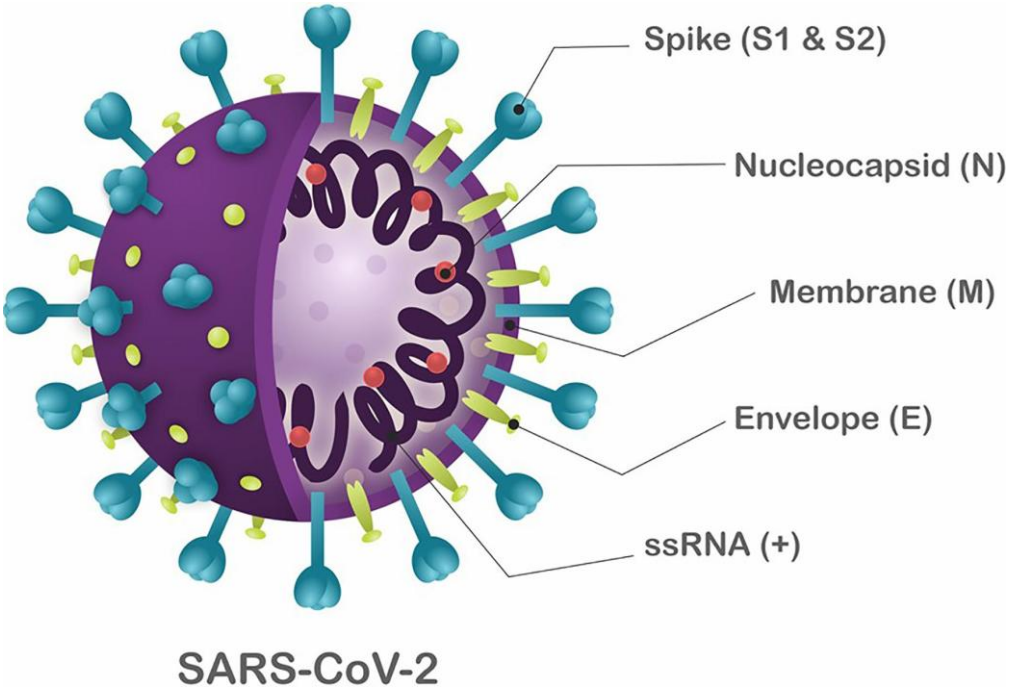

Fig. 1. Schematic structure of SARS-CoV-2. The viral structure is primarily formed by the structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S, M, and E proteins are all embedded in the viral envelope, a lipid bilayer derived from the host cell membrane. The N protein interacts with the viral RNA in to the core of the virion (43).

1.1.2. Variants of SARS-CoV-2

SARS-CoV-2 exhibits substantial genetic variability, facilitating the emergence of mutations and new genetic variants. Since its initial identification, the virus has undergone continuous evolution, leading to the appearance of several variants of concern (VOCs) with significant public health implications. Some of these variants have demonstrated increased transmissibility, more severe clinical outcomes, and an enhanced ability to evade the immune response (44). The WHO named the major SARS-CoV-2 variants using letters from the Greek alphabet. Thus, the first identified

variant under this naming system was Alpha in 2020, followed by Beta, Gamma, Delta, and Omicron (45).

The experiences from the COVID-19 pandemic confirm that the clinical manifestations of acute infections during different epidemic waves differ from one another (46). This is explained by the fact that SARS-CoV-2 has undergone important changes since it was first detected in Wuhan, China, in 2019 (47). The differences between SARS-CoV-2 variants are mainly due to a wide range of recombinations, point mutations, deletions, and amino acid exchanges occurring in the S protein receptor-binding domain. These types, identified as separate variants due to significant genetic changes, often have different transmission capabilities, disease courses, and immune-evading properties (44). Following the transmission of SARS-CoV-2 to humans, the virus's initial evolution was characterized by limited adaptation and minimal phenotypic changes (48). The first significant alteration, a mutation in the spike protein, conferred approximately a 20% growth advantage and rapidly became dominant in Europe (49). From October 2020 onwards, new SARS-CoV-2 variants gradually emerged, accumulating numerous mutations, particularly in the spike protein gene.

The first of these variants was the Alpha variant. This virus was 50-75% more transmissible than earlier SARS-CoV-2 strains. Its global spread can be traced to the end of 2020 and continued until the appearance of the Delta variant (18). The Alpha variant differs from the original virus in 19 mutations in its genome (50), including mutations that provide replication advantages. The Beta and Gamma variants of SARS-CoV-2 were first identified in late 2020 in South Africa and Brazil, respectively, and have since been classified as VOC due to their potential for increased transmissibility and immune evasion. These variants caused endemic-level infections (18). Mutations in the S protein of the Beta variant substantially diminished the neutralizing efficacy of antibodies induced by either natural infection or vaccination, indicating a marked ability of the variant to evade immune responses (51). The Gamma variant carries mutations within the RBD of the S protein that are also present in the Alpha variant. These alterations have been associated with increased binding affinity to the ACE2 receptor and enhanced transmissibility (52).

The next variant to emerge was the Delta variant, which caused the pandemic from December 2020 until the emergence of the Omicron variant (53, 54). The Delta

variant was more transmissible than previous SARS-CoV-2 strains. Studies showed that the Delta variant was associated with more severe disease, particularly in unvaccinated individuals. It was also more resistant to the vaccines, though full vaccination still offered protection against severe outcomes. The Delta variant often caused a greater number of breakthrough infections, especially in areas with low vaccination rates. Its symptoms were similar to the Alpha variant, including fever, cough, and fatigue, but it was found to be more likely to lead to hospitalization (53-55).

The Omicron variant contains 50 new mutations compared to the original strain (56). The Omicron variant, first detected in South Africa in November 2021, quickly became the dominant strain worldwide due to its highly transmissible nature and ability to evade some immune responses. Variants, notably Omicron, exhibit shorter incubation and increased transmissibility, significantly raising global case numbers (16, 18-21). Omicron's rapid spread led to a surge in cases, even in highly vaccinated populations. Despite its increased transmissibility, the severity of illness was generally lower than that of Delta, especially among those who had been vaccinated or previously infected (57). However, the Omicron variant was associated with increased reinfection rates and breakthrough infections (58).

The basic reproduction number (R0), an indicator describes the internal transmissibility of a virus, was estimated at aroundapproximately 2.5 during the initial outbreak of SARS-CoV-2 (59). Interestingely, this value increased to around 5 with the emergence of the Delta variant (60), and exceeded 8 following the spread of the Omicron variant (61), reflecting a marked escalation in the transmissibility of successive viral lineages. This demonstrates that the emergence of successive SARS-CoV-2 variants has progressively increased the basic reproduction number, indicating a substantial rise in transmissibility.

1.1.3. Clinical features and diagnostic of COVID-19

The clinical manifestations of COVID-19 exhibit considerable variability, ranging from asymptomatic cases to severe, life-threatening illness (62). The majority of COVID-19 patients present with common symptoms such as fever, cough (with or without sputum), dyspnea, sore throat, nasal congestion, chills, fatigue, myalgia, arthralgia, dizziness, and chest tightness (63-69). Less frequent symptoms include headache, diarrhea, abdominal

pain, vomiting, chest pain, and rhinorrhea (70-73). Fever, cough, and fatigue are considered the most prevalent clinical signs (74, 75).

Bilateral pneumonia is commonly observed, while unilateral involvement is less frequent. Typical chest CT findings include bilateral ground-glass opacities, patchy consolidations, and multilobar involvement (76-79). Laboratory abnormalities often include normal or reduced white blood cell count, lymphopenia, and thrombocytopenia (80, 81).

Beyond medical history, clinical assessment, and imaging, more specific diagnostic approaches can be utilized in diagnostics of COVID-19. These include the detection of the virus's antigen and/or RNA. For rapid diagnosis, antigen tests have been developed that provide results within 15 minutes. The coronavirus infection is confirmed with a positive antigen test. Because a negative rapid test result does not exclude infection, it should be confirmed by PCR testing for viral RNA. Both antigen and RNA tests require nasal and/or throat swab specimens. Factors such as vaccination status, inadequate sampling, or the timing of sample collection may influence test results (82). Additionally, SARS-CoV-2 specific immunglobulin M and immunglobulin G antibodies can be detected in blood samples, helping to determine whether an active infection is present and whether the patient has had a prior COVID-19 infection (83).

1.2. Long-term consequences of COVID-19

1.2.1. Pathomechanism

Most people generally recover within a few weeks after the acute phase of COVID-19; however, some may experience long-term effects following the infection, which are commonly referred to as 'post-COVID condition' or long COVID. Although there is still no consensus on the nomenclature and definition, the National Institute for Health and Care Excellence defines long COVID as COVID-19 symptoms lasting 4-12 weeks, and post-COVID-19 syndrome when symptoms persist for more than 12 weeks after the infection (84).

Post-COVID-19 condition is characterized by a wide spectrum of clinical manifestations, potentially affecting multiple organ systems (85). The severity of the acute COVID-19 infection, as well as the type of medical care received - particularly

intensive care unit treatment - can influence the clinical characteristics and course of post-COVID-19. The long-term effects of various SARS-CoV-2 variants, as well as the clinical consequences of reinfection, have not yet been fully elucidated. Potential contributory mechanisms include direct organ damage caused by SARS-CoV-2, dysregulated inflammatory responses, effects of therapeutic interventions (especially hospitalization and ICU care), and complications following a critical illness (86). In addition, the manifestation, progression, and outcomes of post-COVID-19 are influenced by other factors such as socioeconomic determinants, preexisting comorbidities, and the long-term consequences of critical illness (87).

A critical immunopathological mechanism involves impaired type I interferon (IFN-I) signaling, commonly observed in severe COVID-19 cases. This impairs viral clearance and triggers emergency myelopoiesis, leading to an increased presence of monocytes, neutrophils, and myeloid progenitors in peripheral blood. Consequently, a reduction in organ-specific effector immune cells, including lymphocytes and dendritic cells, is often observed (88).

The immune response is further compromised by low somatic hypermutation rates, resulting in the expansion of plasmablasts capable of recognizing a broader antigenic spectrum. Autoantibody production, particularly anti-SARS-CoV-2 IgG with enhanced receptor-binding affinity, may drive cytokine overproduction and a heightened inflammatory response (88).

Among patients who survive sepsis or critical illness, the long-term prognosis is often unfavorable. This may be attributed to sustained cytokine elevation caused by dysregulated immune responses during the acute phase, exhaustion of memory lymphocyte subsets, the expression of lymphocyte exhaustion markers, and epigenetic reprogramming (88).

Emerging literature suggests that the long-term sequelae of COVID-19 are driven by the convergence of immune dysregulation, microbiome imbalance, autoimmunity, and endothelial dysfunction (88).

The pathophysiology of the post-COVID-19 condition is partly attributable to the direct effects of the SARS-CoV-2 virus, the host immune response during the acute phase of infection, and the long-term organ-specific and functional sequelae associated with severe disease.

1.2.2. Post-acute sequelae of COVID-19

Post-COVID-19 condition is characterized by multisystem involvement, including manifestations in the central nervous system (e.g., anosmia, cognitive impairment), the respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems, as well as symptoms of fatigue and depression (89, 90). These alterations are likely the result of a complex interplay between disease-induced stress responses, endothelial dysfunction, and immune dysregulation. Among individuals recovering from critical COVID-19, there is an increased risk of developing cerebrovascular diseases, neurodegenerative disorders, and peripheral nervous system alterations. Additionally, a higher prevalence of depressive and stress-related disorders, as well as myalgic encephalomyelitis/chronic fatigue syndrome, has been reported (88). Sleep problems and skin issues, such as telogen effluvium, are common (64, 75). Olfactory dysfunction results mainly from viral-induced neuronal inflammation via ACE2 receptor pathways (91, 92).

Post-COVID-19 respiratory symptoms commonly include persistent dyspnea, cough, and restrictive ventilatory abnormalities with up to 7% of patients requiring home oxygen therapy (93, 94). Pulmonary imaging techniques often reveal ground-glass opacities and fibrosis, reflecting the consequences of pulmonary inflammation (93). Cardiovascular sequelae involve myocarditis, arrhythmias, and right ventricular dysfunction, with myocarditis persisting in about 60% of patients two months post-infection, though less common in asymptomatic athletes (93, 95, 96). Post-COVID-19 renal complications may include residual effects of acute kidney injury that occurs in approximately 20% of hospitalized COVID-19 patients and in over 50% of those with critical illness (88). Musculoskeletal sequelae such as joint stiffness, arthralgia, and myalgia are also frequently reported. Additionally, bone mineral density loss and persistent joint pain have been documented (88). Gastrointestinal manifestations during the post-COVID-19 phase may include gastroenteritis, pancreatitis, elevated liver enzymes, prolonged cholestasis, and malnutrition. Common symptoms include abdominal pain, nausea, vomiting, and diarrhea, which typically resolve within 3 to 6 months post-infection in up to 90% of patients (88). Viral antigens may persist in the gastrointestinal tract for several months following the acute infection. SARS-CoV-2 infection has also been shown to disrupt the gut microbiota, potentially promoting

inflammation and facilitating opportunistic pathogen overgrowth and dissemination (88).

Patients with a history of COVID-19 infection exhibit an increased risk of perioperative morbidity and mortality. Evidence suggests that the risk of postoperative mortality returns to baseline when elective surgery is performed at least seven weeks after the diagnosis of COVID-19. However, individuals who continue to experience symptoms beyond this seven-week period demonstrate a significantly higher perioperative risk compared to those who are asymptomatic at the time of surgery (97).

Hematologically, hypercoagulability elevates thromboembolic risk, with post-discharge events around 2.5% without prophylaxis. These multisystem sequelae underscore the need for comprehensive long-term management (93).

1.2.3. Sleep disturbances in COVID-19

According to the WHO, sleep disorders are one of the most common post-COVID health issues (98) (Fig. 2). During the COVID-19 pandemic, the global prevalence of sleep disorders was 30-40%, with the highest prevalence (52-75%) among patients infected with COVID-19 (99). It appears that sleep disorders are more common in severe cases of COVID-19 and can persist for months after recovery from the acute illness (100). Despite growing literature on the subject, the role of sleep disorders in long COVID is still not well understood. The recently conducted International Covid Sleep Study-II (ICOSS-II) identified high prevalences of fatigue (61.3%), insomnia (49.6%), and excessive daytime sleepiness (35.8%) as the most important outcomes following the acute condition in patients showing prolonged COVID symptoms (101). However, the significance of the relationship between the type of viral variant (i.e., VOC, which means the viral variants characterized by evidence of increased transmissibility, enhanced pathogenicity, or reduced efficacy of existing diagnostic methods, therapeutics, or immunization strategies, thereby representing a heightened risk to public health) and long COVID symptoms, such as fatigue and sleep disorders, has not yet been fully explored (102). Furthermore, the potential impact of vaccination on the pattern of long COVID symptoms ('phenotype') is still unknown.

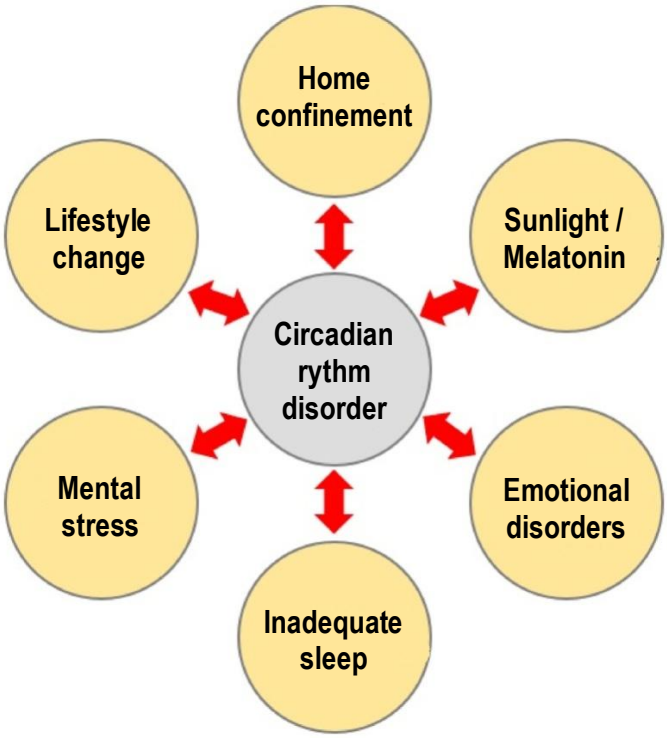

Fig. 2. COVID-19 related factors contributing to poor sleep. Based on prior studies, there are at least 6 major factors that are bidirectionally related to poor sleep: home confinement/quarantine (103, 104), lifestyle disruption (105, 106), daylight exposure and melatonin level (104, 106), circadian misalignment and delayed chronotype (103, 107), emotion dysregulation (104, 108, 109), and increased levels of stress and anxiety with respect to disease vulnerability itself, but also financial, occupational and social consequences of the COVID-19 crisis (110, 111). However, other reports indicate that factors contributing to poor sleep quality are not limited to those mentioned above (112).

1.3. Quality of sleep

The quality and quantity of sleep determine the state of our body and are an important part of our physiological processes, such as the proper functioning of the immune system, maintaining physical and mental capabilities, the functional regeneration of skeletal muscles, metabolic processes, and proper cognitive functions. Sleep deprivation (whether absolute or relative) has been proven to reduce both cognitive and physical

performance. In the long term, it increases the risk of many diseases, such as stroke, diabetes, cardiovascular diseases, obesity, and malignant tumors (112).

The quality of sleep is a significant determinant of health and quality of life. Proper sleep quality is an important factor in maintaining an individual's bio-, psycho-, social-, and cultural functions. This is an important definition both in clinical practice and in sleep-related research. Sleep quality is a complex concept that, because of its multifaceted nature, is difficult to define and quantify (113).

1.3.1. Definition

Sleep quality encompasses many factors, such as total sleep time, the duration of falling asleep, the frequency of awakenings, and other subjective and qualitative aspects. Fundamentally, the factors that determine sleep quality can be divided into two main groups based on whether we influence them. Sleep quality is influenced by both internal and external factors. Internal factors include changes in brain structure and function, age, sex, and overall health status, as well as social determinants. External factors encompass lifestyle, medications, and environmental conditions such as light, noise, and temperature (114).

1.3.2. Consequences of inadequate sleep quality

Suboptimal sleep quality is generally associated with increased healthcare costs, reduced work performance, a higher risk of psychiatric disorders, and an overall decline in health and quality of life. The consequences can be divided into two groups based on their timing. There can be short-term consequences, such as fatigue, drowsiness, reduced performance, irritability, prolonged reaction time, distractibility, etc. If these persist, they can lead to serious consequences (e.g. workplace or traffic accidents). Sleep deprivation, along with the resulting fatigue and exhaustion, are factors that influence psychological state, often leading to anger, anxiety, and frustration. Optimal sleep quality is necessary for the proper functioning of the immune system. Without it, the body's ability to defend against various pathogens decreases, making the individual more susceptible to infections. Sleep deprivation generates and maintains a chronic inflammatory state in the body. This brings us to the second group: the long-term

consequences. These include obesity, hypertension, cardiovascular diseases, hormonal imbalances, metabolic disorders, increased susceptibility to depression, anxiety, and problems related to social and psychosocial life (115-120).

Insufficient sleep quality and its effects on our daily activities are common problems. Poor sleep quality not only causes consequences but can also be a relevant symptom of numerous health conditions. Indirectly, poor sleep quality is associated with increased healthcare costs, decreased work performance, and a higher risk of psychiatric diseases. Consequently, the deterioration of sleep quality has a rather negative impact on both general health and society (84).

1.3.3. Measurement of sleep quality - objective methods

Inadequate sleep has been recognized as a potential risk factor for various medical conditions, but it may also manifest as a symptom of underlying diseases. Therefore, assessing patients' sleep quality is essential. Diagnosing poor sleep quality is inherently challenging. Methods for evaluating sleep quality are generally classified into two categories: objective and subjective approaches (121).

Objective assessment of sleep quality is primarily conducted using non-invasive methods. One of the most widely used tools is polysomnography (PSG), a comprehensive diagnostic technique. However, PSG has several limitations: it is expensive, time-consuming to evaluate, and requires specialized expertise, which restricts its accessibility. PSG can diagnose sleep-related movement and breathing disorders, as well as other sleep-related medical conditions. Another objective tool is actigraphy, which tracks movement by measuring limb acceleration in three dimensions to measure sleep-wake patterns and circadian rhythms over days or weeks. The multiple sleep latency test (MSLT) is also used to objectively measure daytime sleepiness and, thus, assess sleep quality. This test requires a full day and consists of five scheduled sleep periods, each separated by two-hour intervals. It is also the standard for diagnosing conditions like narcolepsy and idiopathic hypersomnia, helping determine how quickly the patient fall asleep (sleep latency) and when the rapid eye movement sleep occurs after napping (121).

1.3.4. Measurement of sleep quality - subjective methods

One of the most commonly used subjective methods for assessing sleep quality is the sleep diary, a daily record that tracks sleep patterns and related daily habits to identify factors affecting sleep quality. In addition, an increasing number of validated retrospective questionnaires are now available for evaluating sleep quality.

One of the commonly used questionnaires is the Athens Insomnia Scale (AIS) that helps to quantify sleep difficulties based on the International Classification of Diseases, 10th Revision (ICD-10) criteria. ICD-10 is a global standard developed by the WHO for coding diseases, symptoms, injuries, and causes of death (122). The widely used version of the AIS (i.e. AIS-8) consists of eight items. The first five assess sleep initiation, nighttime awakenings, time of the final awakening, total sleep duration, and overall sleep quality. The remaining three items evaluate the consequences of sleep disturbances, including well-being, daily functioning, and daytime sleepiness. A shorter version, the AIS-5, includes only the first five items (123).

The Insomnia Severity Index (ISI) is also an extensively used self-report questionnaire designed to evaluate both the nighttime and daytime components of insomnia. This seven-item instrument assesses the nature, severity, and functional impact of insomnia symptoms experienced over the preceding two weeks. Specifically, it examines difficulties with sleep initiation, sleep maintenance, and early morning awakenings; satisfaction with current sleep patterns; the extent to which sleep problems interfere with daily functioning; the level of distress or concern caused by sleep difficulties; and the perceived visibility of these issues to others, which may reflect a broader decline in quality of life. Each item is rated on a five-point Likert scale, with higher total scores indicating greater insomnia severity (124).

One widely used instrument is the Mini Sleep Questionnaire (MSQ), which comprises two primary components assessing sleep quality and daytime sleepiness. Originally designed to evaluate excessive daytime sleepiness, the MSQ examines various factors such as the propensity to fall asleep during the day, morning fatigue, snoring, nocturnal awakenings, waking with headaches, and chronic tiredness. Additionally, it considers indicators of disturbed sleep, including difficulty initiating or maintaining sleep, restless sleep, and the use of sleep-inducing medications (125).

The Jenkins Sleep Scale (JSS) is another subjective instrument designed to assess sleep disturbances over a four-week period. It comprises four items that evaluate difficulty initiating sleep, frequency of nocturnal awakenings, ease of returning to sleep after awakenings, and early morning awakenings. Each item is rated on a six-point Likert scale, reflecting the frequency of the specific sleep problem (126).

Also belonging to this category is the Leeds Sleep Evaluation Questionnaire (LSEQ), a ten-item instrument designed to assess changes in sleep quality following psychopharmacological interventions. The questionnaire evaluates four key domains: ease of sleep onset, perceived sleep quality, ease of awakening, and behavior following wakefulness. The LSEQ is particularly well-suited for measuring the effects of various psychoactive substances, including sedatives, antidepressants, anxiolytics, central nervous system stimulants, and antihistamines (127).

The SLEEP-50 is another widely utilized self-report questionnaire designed to assess a broad range of sleep-related disorders and complaints. It comprises nine distinct scales that evaluate conditions such as sleep apnea, insomnia, narcolepsy, restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorders, sleepwalking, and nightmares. In addition, it assesses factors influencing sleep and the impact of sleep disturbances on daily functioning (128).

The Epworth Sleepiness Scale (ESS) is a widely used instrument in clinical practice for evaluating excessive daytime sleepiness. It requires individuals to rate their likelihood of falling asleep in eight everyday situations, using a 4-point scale ranging from 0 (would never doze) to 3 (high chance of dozing). The scores for each item are summed to yield a total ESS score, with values greater than 10 indicating clinically significant daytime sleepiness (129).

Although not specifically designed to assess sleep quality, the Fatigue Severity Scale (FSS) is an important instrument for evaluating fatigue. It measures the extent to which fatigue interferes with an individual's daily activities and lifestyle. Respondents rate each item on a seven-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The overall FSS score is calculated as the mean of all item scores, with higher values reflecting greater fatigue severity. A score of ≥ 4 is generally considered the threshold for clinically significant fatigue, as originally proposed (130).

An essential questionnaire to evaluate sleep quality in clinical practice is the Pittsburgh Sleep Quality Index (PSQI), which is discussed in details in Section 1.3.5.

In summary, self-report questionnaires are valuable tools for assessing sleep quality. They demonstrate adequate psychometric properties, including high internal consistency, test-retest reliability, and convergent as well as divergent validity.

1.3.5. Pittsburgh Sleep Quality Index (PSQI)

1.3.5.1. Main features of PSQI

The PSQI assesses sleep quality over the past month. It was developed by Buysee and colleagues at the University of Pittsburgh, USA in 1988. The PSQI is a reliable questionnaire that provides information on overall sleep quality and sleep abnormalities. Originally designed for clinical purposes, the questionnaire consists of 19 self-assessment items that generate 7 components, which are summed to produce a global score. Additionally, there are 5 more questions to be filled out by a bedmate/roommate, if available. Completion typically takes 5-10 minutes. The PSQI is one of the most widely used and accepted tools in both sleep research and clinical practice, with validated versions available in 56 languages. It effectively distinguishes individuals with sleep-related problems from those without, with a global score of 5 serving as the cutoff point (131).

1.3.5.2. Structure of PSQI

The questionnaire assesses various aspects of sleep. Its 19 questions form 7 components, which are as follows: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep aids, and daytime dysfunctions. Each of the 19 questions is rated on a scale from 0 to 3. The global score is obtained by adding the scores of the 7 components. Therefore, the smallest possible score is 0, and the largest is 21. Those with a score of 5 or lower fall into the optimal sleep quality category. Those with a score higher than 5, however, have poor sleep quality.

The first questions of the questionnaire ask about the patient’s bedtime and wake-up time, sleep onset latency, and total sleep duration. The next section quantifies

physical and psychological events, such as nighttime awakenings, bathroom use, shortness of breath, coughing or snoring, feeling too hot or too cold, nightmares, pain, use of sleep aids, difficulty staying awake during daytime activities, and difficulty maintaining motivation or enthusiasm to complete tasks. These are presented on a semantic scale, with one end marked as very good and the other as very bad. Each question measures a specific area where sleep problems may occur. The 7 components and their related questions are as follows:

- Component 1: subjective sleep quality question (Question 9),
- Component 2: questions related to sleep delay (Questions 2 and 5a),
- Component 3: duration of sleep (Question 4),
- Component 4: usual sleep efficiency assessment (Questions 1, 3, and 4),
- Component 5: questions related to sleep disturbances (Questions 5b-j),
- Component 6: use of sleep aids (Question 7),
- Component 7: daytime dysfunctions assessment (Questions 8 and 9).

The PSQI demonstrated a sensitivity of 89.6%, indicating that it can correctly identify individuals with poor sleep quality in approximately 90% of cases. Furthermore, studies have shown that the PSQI can accurately identify individuals with good sleep quality with a specificity of 86.5% (131).

1.3.5.3. Hungarian validation of PSQI (PSQI-HUN)

The PSQI is an important questionnaire in sleep diagnostics. Given the limited number of validated sleep questionnaires in Hungarian, the Hungarian validation of the PSQI (PSQI-HUN) is particularly significant (Fig. 3). The validation study aimed to assess the reliability and validity of the PSQI-HUN in both clinical and non-clinical samples, including an evaluation of the discriminative and convergent validity of its components. The study involved 231 participants, with 178 in the control group and 53 in the patient group. Control participants with total PSQI scores exceeding 5 were excluded. The group with poor sleep quality (PSQI > 5) demonstrated a diagnostic validity of 89.7% (132).

For the validation process, he original PSQI was first translated into Hungarian and then back-translated into English by an independent translator. The original and back-translated PSQI versions were compared to create the preliminary Hungarian

version. Convergent validity analysis revealed significant correlations between the PSQI-HUN component scores. Results confirmed that both total and individual component scores were higher in the patient group compared to the control group. Overall, the Hungarian validation study demonstrated that the PSQI-HUN is a reliable and valid standardized tool for assessing subjective sleep quality in both clinical and research settings (132).

Pittsburgh Alvásminőség Mutató (PSQI)

Instrukciók:

A következő kérdések az elmúlt hónap során Önre jellemző alvási szokásokra vonatkoznak. Törekedjen arra, hogy válaszai a lehető legpontosabban jellemezzék az elmúlt hónap napjainak és éjszakáinak többségét. Kérem, válaszoljon minden kérdése!

1. Az elmúlt hónapban általában hány órakor feküdt le aludni?
(0-24) _____óra

2. Az elmúlt hónapban általában mennyi időre volt szüksége, hogy elaludjon? _____ perc

3. Az elmúlt hónapban általában hány órakor kelt fel reggel? _____óra
(0-24)

4. Az elmúlt hónapban éjszakánként hány órát töltött ténylegesen alvással?
(Ez különbözhet azon órák számától, amit ágyban töltött) _____óra

Kérem minden kérdésre válassza ki az Önre leginkább jellemző választ:

5. Az elmúlt egy hónapban milyen gyakran volt problémája az alvással, mert Ön…

a. nem tudott elaludni 30 percen belül
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

b. felébredt az éjszaka közepén vagy kora reggel
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

c. ki kellett mennie a mosdóba
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Kétszer vagy több alkalommal egy héten

d. nem tudott könnyedén lélegezni
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

e. köhögött vagy hangosan horkolt
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

f. úgy érezte túl hideg van
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

g. úgy érezte túl melege van
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

h. kellemetlen álmai voltak
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

i. fájdalmai voltak
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

j. viszketést érzett
- ☐ Nem fordult elő az elmúlt hónapban
- ☐ Kevesebbszer, mint egyszer egy héten
- ☐ Egyszer vagy kétszer egy héten
- ☐ Három vagy több alkalommal egy héten

k. ha egyéb indokból, kérem, írja le: _____

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

6. Az elmúlt hónapra vonatkozólag hogy jellemezné az alvását általában?

☐ Nagyon jó
☐ Kevésbé jó
☐ Rossz
☐ Nagyon rossz

7. Az elmúlt hónapban milyen gyakran szedett gyógyszert (receptre felírva vagy recept nélkül), hogy segítse az alvását?

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

8. Az elmúlt hónapban milyen gyakran volt önnek problémája az ébren maradással vezetés, étkezés vagy szociális elfoglaltság közben?

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

9. Az elmúlt hónapban mennyire okozott problémát, hogy fenntartsa az érdeklődését az iránt, hogy elvégezze a feladatait?

☐ Egyáltalán nem okozott problémát
☐ Kis mértékben okozott problémát
☐ Időnként problémát okozott
☐ Nagymértékben problémát okozott

10. Van önnek partnere vagy szobatársa?

☐ Nincs szobatársam vagy hálótársam
☐ Partner/szobatárs a szomszédos szobában
☐ Partner ugyanabban a szobában, de nem ugyanabban az ágyban
☐ Partner ugyanabban az ágyban

11. Amennyiben Önnek van hálótársa vagy szobatársa kérdezze meg őt, hogy milyen gyakran fordult elő az elmúlt hónapban, hogy…
(amennyiben önnek nincs hálótársa vagy szobatársa próbálja meg megbecsülni a megfelelő választ)

a. hangosan horkolt

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

b. hosszú szünet volt a két lélegzetvétele között, amíg aludt

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

c. lábmozgás vagy rángatózás mialatt aludt

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

d. eltévedési epizód vagy zavartság alvás közben

☐ Nem fordult elő az elmúlt hónapban
☐ Kevesebbszer, mint egyszer egy héten
☐ Egyszer vagy kétszer egy héten
☐ Három vagy több alkalommal egy héten

e. egyéb nyugtalanság mialatt aludt, kérem, írja le: _____

2

Fig. 3. Hungarian version of the PSQI questionnaire (132)

2. Objectives

Although acute infections caused by different SARS-CoV-2 variants are known to exhibit distinct symptoms and clinical manifestations, variant-specific long-term consequences remain incompletely understood. **To explore how variant type influences long-term sequelae - as the primary objective of our research - we conducted two retrospective studies** analyzing sleep-related data of patients infected with SARS-CoV-2 during the three major epidemic waves of COVID-19 in Hungary (February-July 2021, August-December 2021, and January-June 2022).

In the first study, we analyzed data from patients who recovered from SARS-CoV-2 infection to address the following aims:

1. To compare self-reported data on sleepiness, fatigue and sleep quality between patients with and without long-term residual symptoms across the three epidemic waves of COVID-19.
2. To compare PSQI data on sleep quality between patients with and without long-term residual symptoms across the three epidemic waves of COVID-19.

In the second study, we analyzed data from patients who recovered from SARS-CoV-2 infection with post-COVID sequelae to address the following aims:

1. To compare acute/post-infection symptoms between patients with good and poor sleep quality across the three epidemic waves of COVID-19.
2. To compare parameters of circadian sleep-wake rhythm between patients with good and poor sleep quality across the three epidemic waves of COVID-19.

3. Methods

3.1. Study 1 - Analysis of sleepiness, fatigue and sleep quality in COVID-19 patients

3.1.1. Study population

Our study (ethical approval number: SE RKEB 147/2022) is based on the retrospective review of 412 cases who were referred to the post-COVID care of the Semmelweis University, Department of Pulmonology between February 2021 and June 2022. Inclusion in the analysis was based on the following criteria:

- acute COVID-19 during either the 3rd (from February 2021 to July 2021; VOC: B.1.1.7, Alpha; N = 135), 4th (from August 2021 to December 2021; VOC: B.1.617.2, Delta; N = 89) or 5th (from January 2022 to June 2022; VOC: B.1.1.529, Omicron; N = 63) major epidemic waves which affected Hungary (133),
- SARS-CoV-2 infection confirmed by PCR and/or a rapid immunoassay test,
- presentation at the post-COVID care > 4 weeks after the acute course of COVID-19, and
- complete medical records on anthropometric and self reported questionnaire data.

A total of 287 cases met the inclusion criteria. Cases were subsequently categorized into epidemic waves based on the timing of COVID-19 onset (Fig. 4).

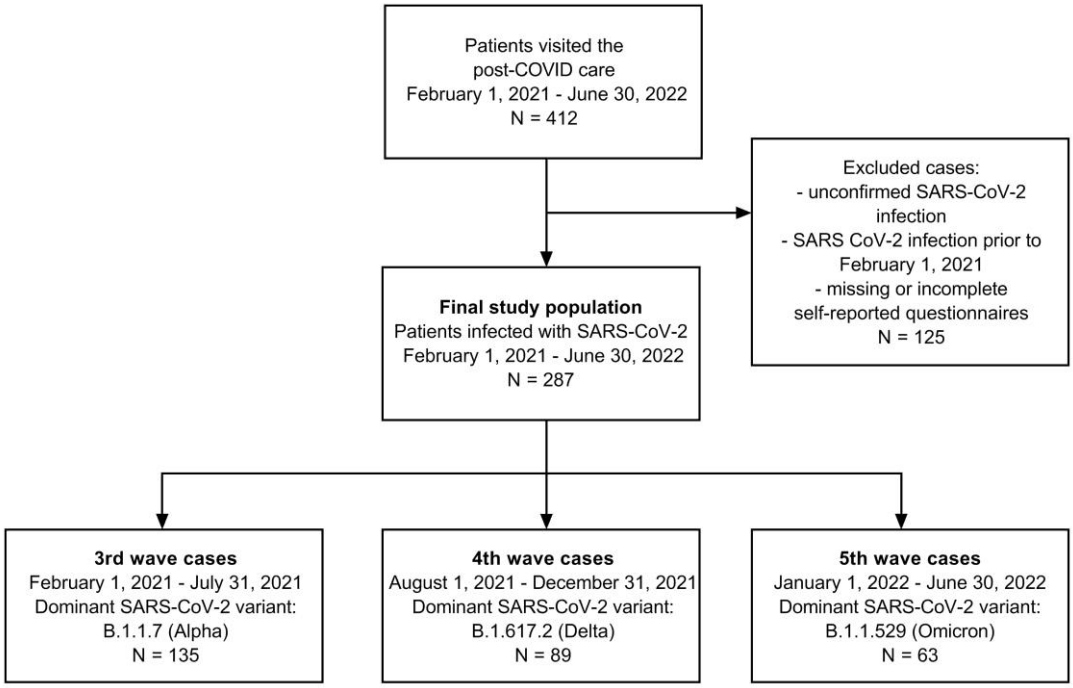

Fig. 4. Study population (Percze AR, Nagy A, Polivka L, et al. Fatigue, sleepiness and sleep quality are SARS-CoV-2 variant independent in patients with long COVID symptoms. Inflammopharmacology. 2023; 31(6): 2819-2825)

3.1.2. Procedures

For statistical analysis, cases were categorized into two groups by expert respiratory physicians as cases with long COVID symptoms (LC group) and asymptomatic cases with clinically resolved COVID-19 (NS group). Categorization was based on the presence of one or more COVID 19 associated symptoms, such as cough, fatigue, dyspnoea, muscle pain, sleep problems, headache, palpitation, loss of taste or smell, sore throat, nasal congestion, nausea, fever and diarrhoea.

The analysis also encompassed self-administered questionnaires, namely the Fatigue Severity Scale (FSS) and the Epworth Sleepiness Scale (ESS) (see Section 1.3.4), as well as the Pittsburgh Sleep Quality Index (PSQI), a well-validated instrument for the reliable assessment of sleep quality (see Section 1.3.5).

3.1.3. Statistic analysis

Continuous variables are expressed as mean ± stand ard error of the mean (SEM). Normality of the data was determined using Kolmogorov-Smirnov test. Differences between groups for continuous data were evaluated in normally distributed data with Student's t-test; otherwise, Mann-Whitney U-test was used. Chi-squared test was applied for comparing categorical variables. All percentage values are expressed for respective subgroups as indicated. For comparison between the waves of different VOCs, we used ANOVA (analysis of variance) with Tukey's post hoc test. A p-value < 0.05 was defined as statistically significant. All analysis was performed using the GraphPad software (GraphPad Prism 5.0 Software, Inc., La Jolla, CA, United States) and SPSS v25 (IBM Corporation, Armonk, NY, United States).

3.2. Study 2 - Analysis of acute/post-infection symptoms and circadian sleep-wake rhythm in COVID-19 patients with post-COVID sequelae

3.2.1. Study population

Our retrospective analysis (ethical approval number: SE RKEB 147/2022) reviewed 412 cases referred to the post-COVID care unit at the Semmelweis University Department of Pulmonology between February 2021 and June 2022. Inclusion in the analysis was based on the following criteria:

- acute COVID-19 during either the 3rd (from February 2021 to July 2021; VOC: B.1.1.7, Alpha; N = 135), 4th (from August 2021 to December 2021; VOC: B.1.617.2, Delta; N = 89) or 5th (from January 2022 to June 2022; VOC: B.1.1.529, Omicron; N = 63) major epidemic waves which affected Hungary (133, 134),
- SARS-CoV-2 infection confirmed by PCR and/or a rapid immunoassay test,
- presentation at the post-COVID care > 4 weeks after the acute course of COVID-19,
- complete medical records on anthropometric and self reported questionnaire data, and
- presence of at least one typical post-COVID-19 symptom, such as fever, cough, dyspnea, fatigue, myalgia, sleep disturbances, headache, palpitations, taste or smell disturbances, sore throat, nasal congestion, nausea, vomiting, or diarrhea.

A total of 189 cases met the inclusion criteria. Cases were subsequently categorized into epidemic waves based on the timing of COVID-19 onset (Fig. 5).

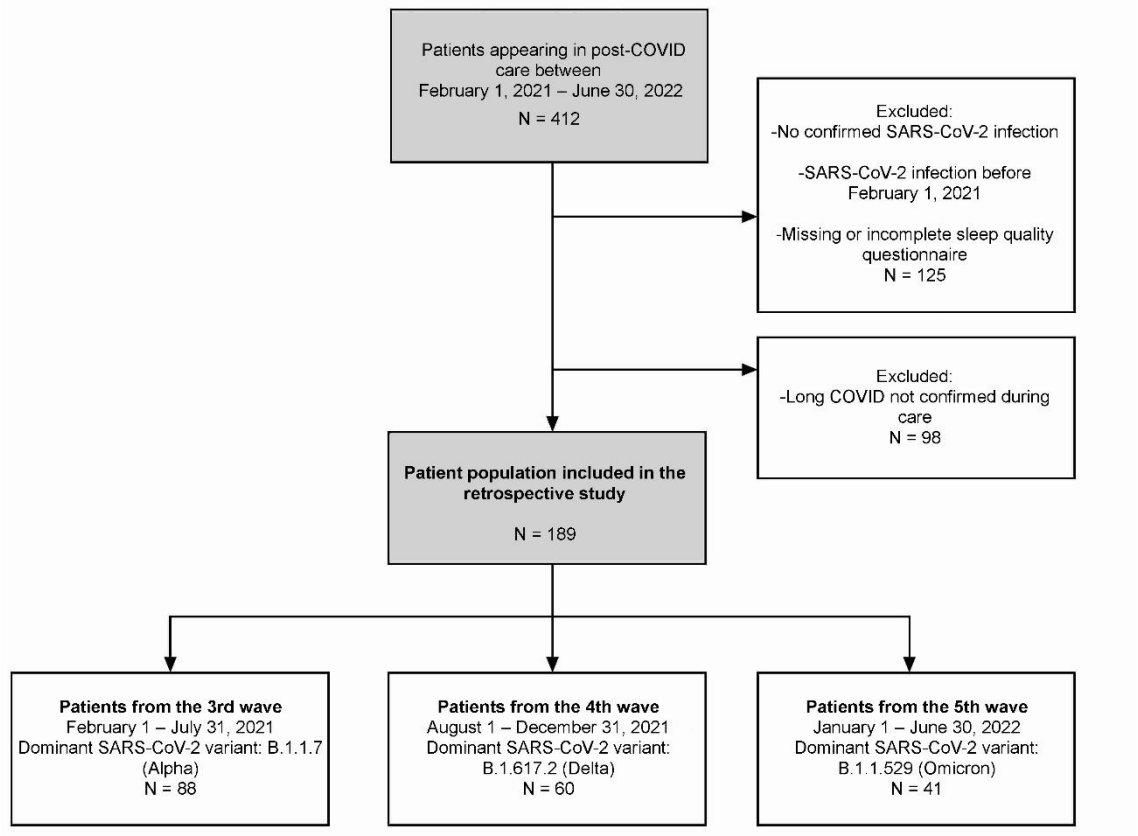

Fig. 5. The patient population included in the retrospective data analysis **(**Percze AR, Bardóczi AB, Nagy A, Vasas Sz, Varga JT, Müller V, Horváth G, et al. Post-COVID-19 symptoms and sleep-wake abnormalities during the COVID-19 pandemic waves in Hungary. Orv. Hetil. 2025;05. 166(21):817-825.)

3.2.2. Procedures

Patient care was conducted in accordance with current national and international guidelines. The clinical evaluation included a standardized symptom checklist, physical examination, pulmonary function testing, and radiological assessment, followed by the formulation of therapeutic recommendations. In addition to the evaluation of symptoms and respiratory impairment, sleep quality was assessed using the validated PSQI questionnaire, available in a Hungarian translation. The detailed description of PSQI is

presented in Chapter 1.3.5. Based on the subsequent analysis of PSQI results, two distinct groups were identified: post-COVID patients with good sleep quality (i.e. PSQI ≤ 5) and those with poor sleep quality (i.e. PSQI > 5).

3.2.3. Statistical analysis

In our statistical analysis, continuous variables were expressed as mean ± SEM. The normality of data distribution was tested using the Kolmogorov-Smirnov test. Differences between groups were evaluated using Student's *t*-test for normally distributed continuous variables, and the Mann-Whitney *U* test for non-normally distributed data. Categorical variables were compared using the chi-square test. All percentage values were presented in relation to the corresponding subgroups. Comparisons between epidemic waves were performed using ANOVA followed by Tukey's post hoc test. A p value of < 0.05 was considered statistically significant. All analyses were performed using GraphPad Prism 5.0 software (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS version 25 (IBM Corporation, Armonk, NY, USA).

4. Results

4.1. Study 1 - Analysis of sleepiness, fatigue and sleep quality in COVID-19 patients

4.1.1. Patient characteristics

The baseline characteristics of the 287 patients with symptoms persisting beyond one month are summarized in Table 1. Overall, the mean age of the study population was 54 years, men were more frequently represented than women (57.5% vs. 42.5%) and the mean body mass index (BMI) was close to 30, indicating that patients were predominantly overweight or obese. Assessment of comorbidities revealed hypertension as the most prevalent condition, followed by chronic respiratory diseases, other cardiovascular diseases, diabetes mellitus, and thromboembolic disorders.

Patients were further analyzed according to the three consecutive COVID-19 waves in Hungary, dominated by the Alpha, Delta, and Omicron variants, and were stratified into long COVID (LC) and symptom-free groups (NS).

From the Alpha-dominated wave, 135 patients were included, of whom 88 presented long COVID symptoms. Age and BMI were nearly identical in LC and ND groups. Interestingely, gender distribution was nearly balanced in the LC group, whereas NS patients were predominantly male. LC patients more frequently had chronic respiratory and thromboembolic diseases, while hypertension, diabetes, and other cardiovascular conditions were more common in NS patients.

From the Delta-dominated wave, 89 patients were included, of whom 60 presented long COVID symptoms. LC patients were slightly younger than NS patients, but no relevant differences in BMI were observed. Chronic respiratory diseases and diabetes were more prevalent among LC patients, whereas hypertension and other cardiovascular diseases were observed more frequently in NS cases. The occurrence of thromboembolic diseases did not differ substantially between groups.

From the Omicron-dominated wave, 63 patients were included, of whom 41 presented long-COVID symptoms. This patients population had the highest mean age among the waves analyzed, while BMI remained similar between LC and NS patients. Hypertension and diabetes were more prevalent in LC patients. In contrast, chronic

respiratory diseases, other cardiovascular conditions, and thromboembolic events occurred more frequently in NS individuals.

Table 1. Characteristics of patients with (LC) and without (NS) long COVID symptoms. Data are presented as the mean ± SEM. BMI = body mass index. *Cardiovascular disease other than hypertension. (Percze AR, Nagy A, Polivka L, et al. Fatigue, sleepiness and sleep quality are SARS-CoV-2 variant independent in patients with long COVID symptoms. Inflammopharmacology. 2023; 31(6): 2819-2825)

	All patients N = 287	**3rd wave (Alpha) N = 135**		**4th wave (Delta) N = 89**		**5th wave (Omicron) N = 63**	
		LC (88)	**NS (47)**	**LC (60)**	**NS (29)**	**LC (41)**	**NS (22)**
Age (years)	53.9 ± 0.9	54.2 ± 1.3	55.4 ± 2.1	50.1 ± 2.1	55.6 ± 3.3	55.7 ± 2.7	53.7 ± 3.3
Gender (N, %)							
Male	165 (57.5)	43 (48.9)	33 (70.2)	30 (50)	22 (75.9)	21 (51.2)	16 (72.7)
Female	122 (42.5)	45 (51.1)	14 (29.8)	30 (50)	7 (24.1)	20 (48.8)	6 (27.3)
BMI (kg/m^2)	29.3 ± 0.4	29.9 ± 0.7	29.0 ± 0.7	30.1 ± 1.1	28.9 ± 1.0	27.6 ± 0.9	29.3 ± 1.3
Comorbidities (N, %)							
Hypertension	133 (46.3)	39 (44.3)	26 (55.3)	23 (38.3)	14 (48.3)	23 (56.1)	8 (36.4)
Chronic respiratory disease	59 (20.6)	20 (22.7)	2 (4.3)	13 (21.6)	5 (17.2)	12 (29.3)	7 (31.9)
Cardiovascular disease*	48 (16.7)	11 (12.5)	7 (14.8)	9 (15)	8 (27.6)	8 (19.5)	5 (22.7)
Diabetes	42 (14.6)	6 (6.8)	8 (17)	8 (13.3)	2 (6.9)	16 (39)	2 (9.1)
Thromboembolic disease	13 (4.5)	5 (5.7)	2 (4.3)	2 (3.3)	2 (6.9)	0 (0)	2 (9.1)

4.1.2. Sleep quality assessment by questioning regarding symptoms vs. the PSQI questionnaire

To assess sleep quality in patients recovered from SARS-CoV-2 infection, two distinct approaches were used. First, a simple questioning regarding symptoms, which focused on whether the individual had complaints of drowsiness or insomnia. Based on this approach, 81 patients (28.2%) reported increased drowsiness or insomnia, whereas 206 patients (71.8%) reported optimal sleep quality. In the LC patient goup, 81 patients

(42.9%) reported increased drowsiness or insomnia, whereas 108 patients (57.1%) reported optimal sleep quality.

Sleep quality was also assessed using the PSQI questionnaire in the same groups. A PSQI score > 5 was considered as poor sleep quality. Based on this second approach, 141 patients (49.1%) were identified with poor sleep quality, while 146 patients (50.9%) had adequate sleep quality. In the LC patient goup, 118 patients (62.4%) were identified with poor sleep quality, while 71 patients (37.6%) had adequate sleep quality. Therefore, the PSQI survey proved to be significantly more effective than simple questioning regarding symptoms in identifying poor sleep quality (Table 3).

Table 2. Sleep quality assessment by questioning regarding symptoms vs. the PSQI questionnaire in patients recovered from SARS-CoV-2 infection. $p < 0.05$ vs. questioning. (Percze AR, Bardóczi AB, Nagy A, et al. Long COVID sleep disorders in pulmonary medicine. [Long COVID alvászavarok a tüdőgyógyászati gyakorlatban.] Med Thorac. 2024; 77: 45–53. [Hungarian])

		Questioning regarding symptoms	**PSQI questionnaire**
All patients	Poor sleep (N, %)	81 (28,2%)	141 (49,1%)*
	Good sleep (N, %)	206 (71,8%)	146 (50,9%)*
Long COVID patients	Poor sleep (N, %)	81 (42,9%)	118 (62,4%)*
	Good sleep (N, %)	108 (57,1%)	71 (37,6%)*

4.1.3. Fatigue, sleepiness, and sleep quality in patients recovered from SARS-CoV-2 infection across the three epidemic waves of COVID-19

Concerning fatigue, sleepiness, and sleep for the whole length of the 3 epidemic waves, mean scores of FSS, ESS, and PSQI were 4.79 ± 0.12, 7.45 ± 0.33, and 7.46 ± 0.27, respectively for LC patients, significantly higher than for asymptomatic patients (2.85 ± 0.16, 5.23 ± 0.32 and 4.26 ± 0.29, respectively; $p < 0.05$ for all vs. LC) (Fig. 7).

Considering the standard cutoff levels of FSS, ESS, and PSQI, 71.3%, 24.5%, and 62.8% of long-COVID patients revealed problematic fatigue, increased sleepiness, and poor sleep quality, respectively. These scores were 26.3%, 7.4%, and 23.1% for asymptomatic patients, respectively ($p < 0.05$ for all vs. LC).

To assess the unique characteristics of predominant VOCs in the three epidemic waves, the differences in fatigue, sleepiness, and sleep quality data among the three waves were analyzed. In all three waves, FSS mean scores exceeded the normal range for long-COVID groups but showed no significant inter-wave differences. In addition, FSS mean scores were significantly higher, and the prevalence of problematic fatigue was approximately three times higher in the LC than in the NS groups in all three waves.

Concerning sleepiness, ESS mean scores were in the normal range, although significantly higher numerically for LC than NS groups in all three waves. In connection with sleep quality, PSQI mean scores exceeded the normal range for LC groups in all waves, which increase was also seen for NS group in the 5th wave. PSQI mean scores were significantly higher, and the prevalence of poor sleep quality was 2 to 4 times higher for LC than NS groups in all waves. However, PSQI scores showed no significant inter-wave differences.

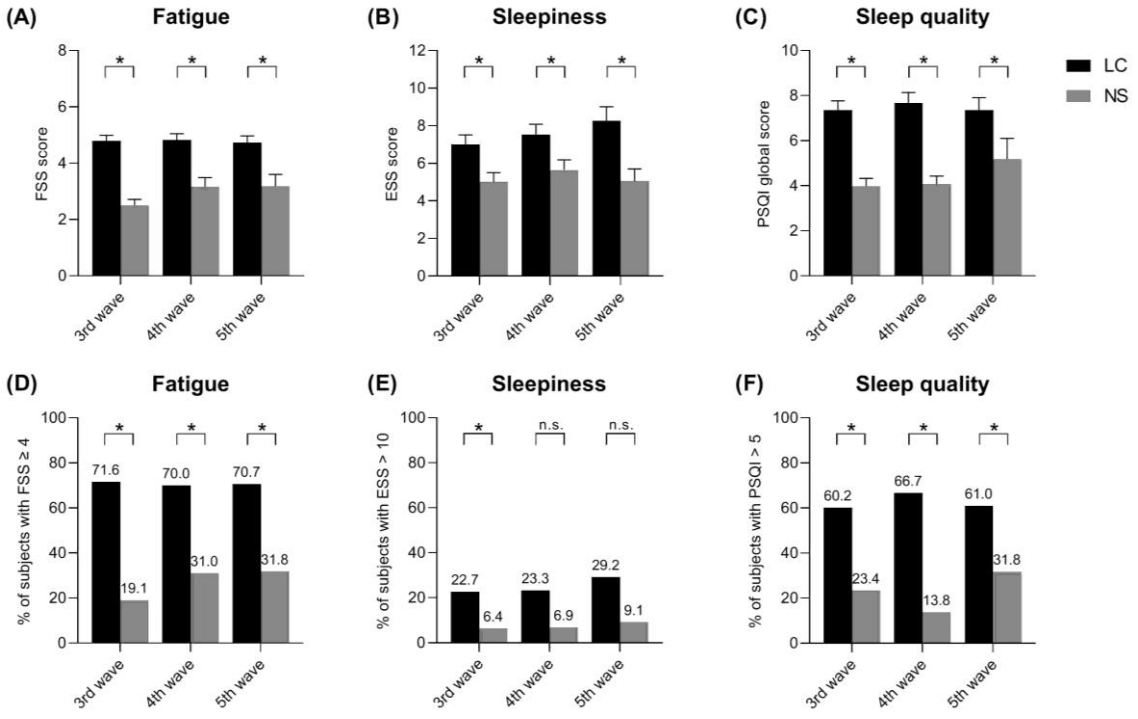

Fig. 6. Fatigue (A, D), sleepiness (B, E) and sleep quality (C, F) in patients with (LC) and without (NS) long COVID symptoms. Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) data are presented as mean ± SEM on Figure A-C, whereas Figure D-F illustrate the percentage of subjects exceeding the standard cut-off values. See Table 1 for n values. *$p < 0.05$ (Percze AR, Nagy A, Polivka L, et al. Fatigue, sleepiness and sleep quality are SARS-CoV-2 variant independent in patients with long COVID symptoms. Inflammopharmacology. 2023; 31(6): 2819-2825)

4.1.4. PSQI analysis of sleep quality in patients recovered from SARS-CoV-2 infection across the three epidemic waves of COVID-19

To further reveal possible unique characteristics of the epidemic three waves, the differences between PSQI component scores, each assessing a specific feature of sleep, were analyzed. Component scores for the LC and NS groups showed no significant differences across the 3 waves. In the 3rd and 4th waves, PSQI component scores were significantly higher for LC than NS groups. However, as a minor difference in the 5th wave, component scores were significantly higher in three categories only (“Subjective sleep quality”, “Sleep onset latency” and “Daytime dysfunction”), but not in others (“Sleep duration”, Sleep efficiency”, “Sleep disturbances” and “Hypnotics use”) for LC than NS groups (Fig. 6).

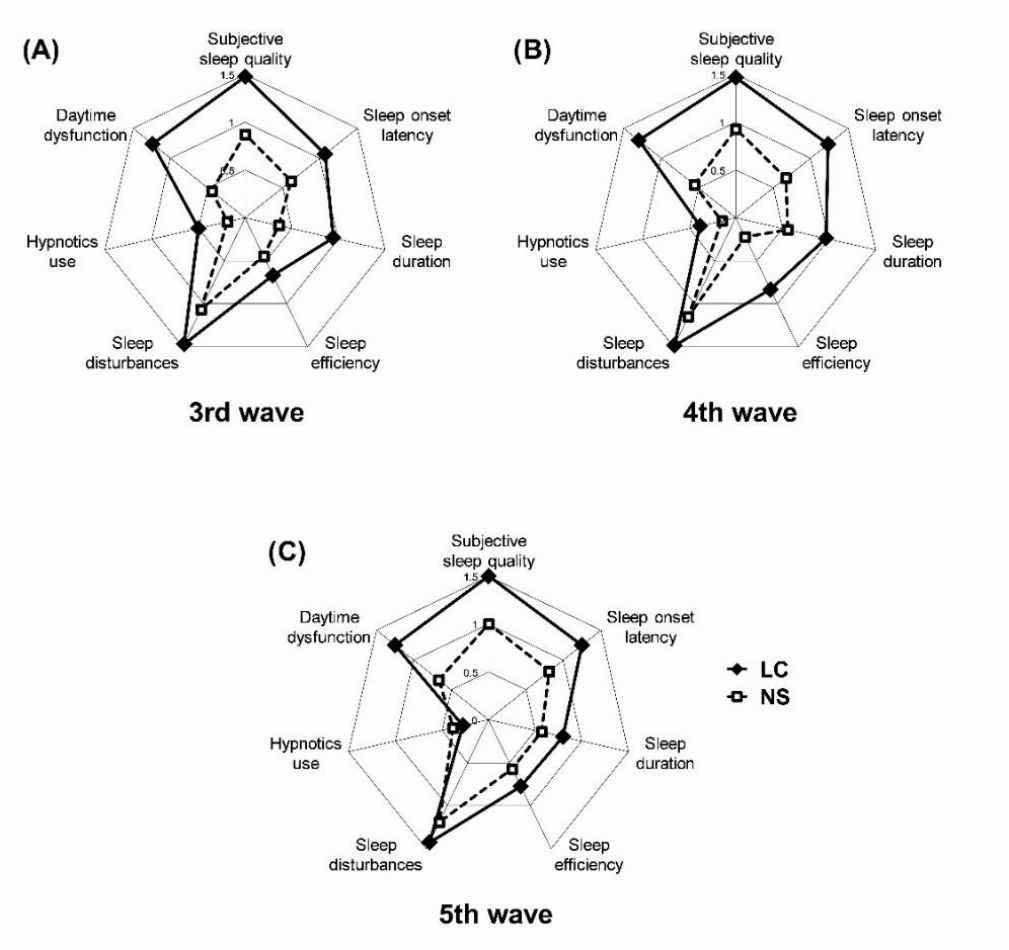

Fig. 7. Radar plots showing sleep quality profiles of patients who were infected with SARS-CoV-2 during the 3rd (A), 4th (B), and 5th waves (C) of COVID-19. Markers show means of Pittsburgh Sleep Quality Index component scores in patients with (LC) and without (NS) long COVID symptoms. See Table 1 for n values. (Percze AR, Nagy A, Polivka L, et al. Fatigue, sleepiness and sleep quality are SARS-CoV-2 variant independent in patients with long COVID symptoms. Inflammopharmacology. 2023; 31(6): 2819-2825)

4.2. Study 2 - Analysis of acute/post-infection symptoms and circadian sleep-wake rhythm in COVID-19 patients with post-COVID sequelae

4.2.1. Patient characteristics

The baseline characteristics of the 189 patients who remained symptomatic for more than one month are summarized in Table 1. Across all three COVID-19 waves, the gender distribution was approximately equal, and the mean age ranged from 50 to 55 years. Based on mean BMI, patients were predominantly classified as overweight or obese.

Table 3. Characteristics of patients in the three epidemic waves of COVID-19 in Hungary (n = 189). **(**Percze AR, Bardóczi AB, Nagy A, et al. Post-COVID-19 symptoms and sleep-wake abnormalities during the COVID-19 pandemic waves in Hungary. Orv. Hetil. 2025;05. 166(21):817-825.)

	3rd wave (Alpha)	**4th wave (Delta)**	**5th wave (Omicron)**
All cases (N)	88	60	41
Male (N, %)	43 (48,9)	30 (50)	21 (51,2)
Female (N, %)	45 (51,1)	30 (50)	20 (48,8)
Age (years)			
Mean ± SEM	54,2 ± 1,3	50,1 ± 2,1	55,7 ± 2,7
Min.	22	25	19
Max.	81	83	91
BMI (kg/m²)			
Mean ± SEM	29,9 ± 0,7	30,1 ± 1,1	27,6 ± 0,9
Min.	15,2	16,3	16,9
Max.	45,3	64,4	41,2

4.2.2. Prevalence of acute/post-infection symptoms

The prevalence of clinical symptoms was significantly higher during the acute phase of COVID-19 than in the post-COVID period; however, this difference decreased across successive pandemic waves (Table 4).

During the acute phase, fatigue was the most common symptom in all three variant-dominated waves, followed by fever, cough, dyspnoea, and sleep disturbance. Overall, the prevalence of acute symptoms were lower in the Delta and particularly in the Omicron wave compared with the Alpha wave. Muscle pain was common during Alpha and Delta infections, whereas palpitations emerged as a more frequent acute symptom in the Omicron wave. Nausea/vomiting was the least prevalent symptom across all variants.

In the post-COVID period, fatigue remained the most frequent symptom in all three waves, although at a lower prevalence than during acute infection. Respiratory symptoms, sleep disturbance, and palpitations were also common, with their relative importance differing by variant. Sleep disturbance consistently ranked among the most frequent post-COVID complaints in all waves. Over time, the prevalence of dyspnoea decreased across waves, while cough and palpitations became more frequent, particularly during the Omicron wave.

Table 4. Prevalence of acute/post-infection symptoms during the three epidemic waves of COVID-19 in Hungary (n = 159). **(**Percze AR, Bardóczi AB, Nagy A, et al. Post-COVID-19 symptoms and sleep-wake abnormalities during the COVID-19 pandemic waves in Hungary. Orv. Hetil. 2025;05. 166(21):817-825.)

	3rd wave (Alpha)		**4th wave (Delta)**		**5th wave (Omicron)**	
	Acute COVID-19	**Post-COVID-19**	**Acute COVID-19**	**Post-COVID-19**	**Acute COVID-19**	**Post-COVID-19**
Symptoms (N, %)						
Fever-subfebrility	74 (84,1)	4 (4,5)	50 (83,3)	1 (1,7)	31 (75,6)	1 (2,4)
Cough	72 (81,8)	30 (34,1)	45 (75)	26 (43,3)	28 (68,3)	19 (46,3)
Dyspnea	70 (79,5)	40 (45,5)	46 (76,7)	26 (43,3)	31 (75,6)	14 (34,1)
Fatigue	80 (90,9)	57 (64,8)	56 (93,3)	37 (61,7)	35 (85,4)	27 (65,9)
Myalgia	59 (67)	25 (28,4)	38 (63,3)	12 (20)	20 (48,8)	12 (29,3)
Sleep disturbance	67 (76,1)	38 (43,2)	43 (71,7)	26 (43,3)	24 (58,5)	17 (41,5)
Headache	40 (45,5)	10 (11,4)	31 (51,7)	9 (15)	13 (31,7)	8 (19,5)
Palpitations	46 (52,3)	21 (23,9)	28 (46,7)	23 (38,3)	21 (51,2)	22 (53,7)
Smell-taste disorder	45 (51,1)	11 (12,5)	33 (55)	8 (13,3)	14 (34,1)	3 (7,3)
Sore throat	39 (44,3)	8 (9,1)	20 (33,3)	4 (6,7)	14 (34,1)	2 (4,9)
Nasal congestion	47 (53,4)	16 (18,2)	27 (45)	13 (21,7)	14 (34,1)	8 (19,5)
Nausea and vomiting	22 (25)	1 (1,1)	12 (20)	2 (3,3)	3 (7,3)	0 (0)
Diarrhea	35 (39,8)	1 (1,1)	21 (35)	5 (8,3)	7 (17,1)	0 (0)

4.2.3. Sleep quality and its connection to hospitalization during acute COVID-19 in long COVID patients

The majority (N = 130, 68.8%) of patients with long COVID symptoms received hospital treatment, whereas only 59 (31.2%) patients were not hospitalized during the acute phase of infection. The PSQI assessment indicated that among patients without hospital care, 49 (83.1%) had poor sleep quality, while 10 patients (16.9%) had optimal sleep quality. Among the patients who received hospital care, 93 (71.5%) had poor sleep quality, while 37 patients (28.5%) had good sleep quality (Fig. 8).

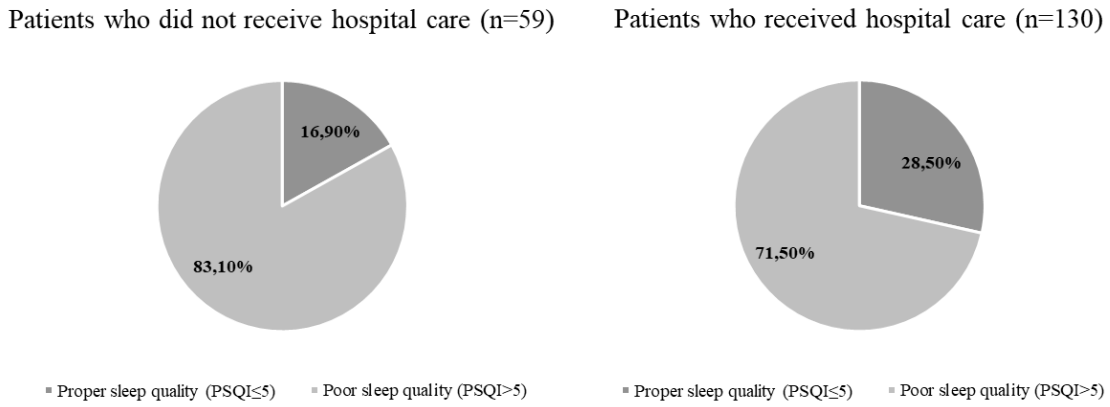

Fig. 8. Sleep quality and its connection to hospitalization during acute COVID-19 in long COVID patients. (Percze AR, Bardóczi AB, Nagy A, et al. Long COVID sleep disorders in pulmonary medicine. [Long COVID alvászavarok a tüdőgyógyászati gyakorlatban.] Med Thorac. 2024; 77: 45–53. [Hungarian])

4.2.4. Prevalence of acute/post-infection symptoms in long COVID patients with good and poor sleep quality

To explore the relationship between patient-reported post-COVID-19 symptoms and impaired sleep quality, we examined differences in symptom profiles between groups with adequate and poor sleep quality across the Alpha, Delta, and Omicron waves of COVID-19 (Fig. 9). In the assessment of sleep quality, a global PSQI score > 5 was considered indicative of poor sleep quality. The high prevalence of poor sleep quality

among patients reporting post-COVID-19 symptoms has already been described in our prior study.

Although the prevalence of post-COVID-19 symptoms was generally higher among patients with poor sleep quality than among those with adequate sleep quality across all three waves, the differences showed considerable heterogeneity among the COVID-19 waves caused by the Alpha, Delta, and Omicron variants.

When comparing the subgroups with adequate and poor sleep quality, fatigue - the most common post-COVID-19 symptom - was observed at a significantly higher rate only among patients with poor sleep quality in the Alpha (48.6% vs. 75.5%; $p < 0.05$) and Delta variant waves (30% vs. 77.5%; $p < 0.05$), whereas high prevalence rates were found in both subgroups during the Omicron variant wave (75% vs. 60%; NS).

Cough and dyspnea, the most frequent respiratory post-COVID-19 symptoms, were identified more often in the poor sleep quality subgroup across all three variants. In contrast, palpitation showed a low prevalence in both the adequate and poor sleep quality subgroups during the Alpha variant wave (22.8% vs. 24.5%; NS), whereas a significantly higher prevalence was observed among patients with poor sleep quality during the Delta variant wave (15% vs. 50%; $p < 0.05$). During the Omicron variant wave, palpitation was frequent in both subgroups (50% vs. 56%; NS). Other symptoms such as headache, anosmia/ageusia, muscle pain, sore throat, and gastrointestinal symptoms varied in prevalence but generally followed the trend of being more common in patients with inadequate sleep quality.

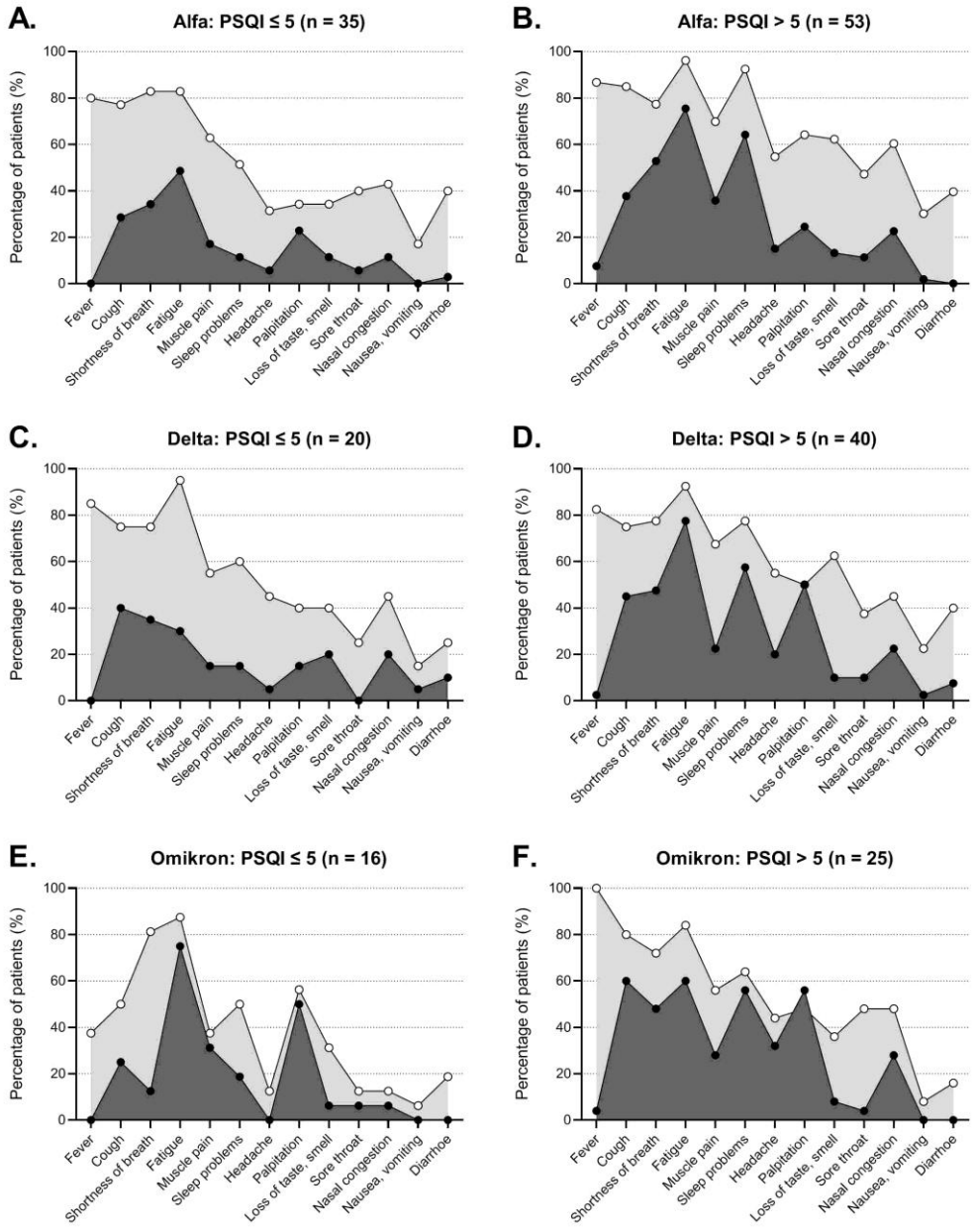

Fig. 9. Prevalence of acute COVID-19 symptoms (o) and post-COVID-19 symptoms (●) in long COVID patients during the epidemic waves caused by the Alpha, Delta, and Omicron variants. The figure separately shows patient groups with adequate (PSQI ≤ 5; Panels A, C, and E) and inadequate sleep quality (PSQI > 5; Panels B, D, and F) for each variant. (Percze AR, Bardóczi AB, Nagy A, et al. Post-COVID-19 symptoms and sleep-wake abnormalities during the COVID-19 pandemic waves in Hungary. Orv. Hetil. 2025;05. 166(21):817-825.)

4.2.5. Characteristics of sleep-wake rhythm

To examine changes in the sleep-wake rhythm, we analyzed patients' bedtime, sleep onset latency, wake-up time, and sleep duration during the COVID-19 epidemic waves caused by the Alpha, Delta, and Omicron variants (Figure 3). Data referring to the month preceding the assessment were collected from patients with post-COVID-19 complications using a self-administered questionnaire. During the analysis, the sleep-wake rhythms of patient subgroups with adequate sleep quality (PSQI $\leq$ 5) and poor sleep quality (PSQI > 5) were compared based on timing and duration parameters of sleep.

With respect to bedtime, a significant difference between patients classified into the adequate and poor sleep quality subgroups was observed only during the Omicron variant wave, indicating a shift toward later bedtimes (21.6 ± 0.4 vs. 22.6 ± 0.2 h; $p < 0.05$) (Figure 3, Panel A).

In contrast, comparison of wake-up times between these subgroups revealed a difference only during the Alpha variant wave, reflecting an earlier wake-up time (6.1 ± 0.2 vs. 5.5 ± 0.2 h; $p < 0.05$) (Figure 3, Panel C).

More pronounced differences were observed when comparing sleep onset latency and total sleep duration between patients with adequate and poor sleep quality. Across all three variants, poor sleep quality was associated with a significant prolongation of sleep onset latency and a significant reduction in total sleep duration (Figure 3, Panels B and D).

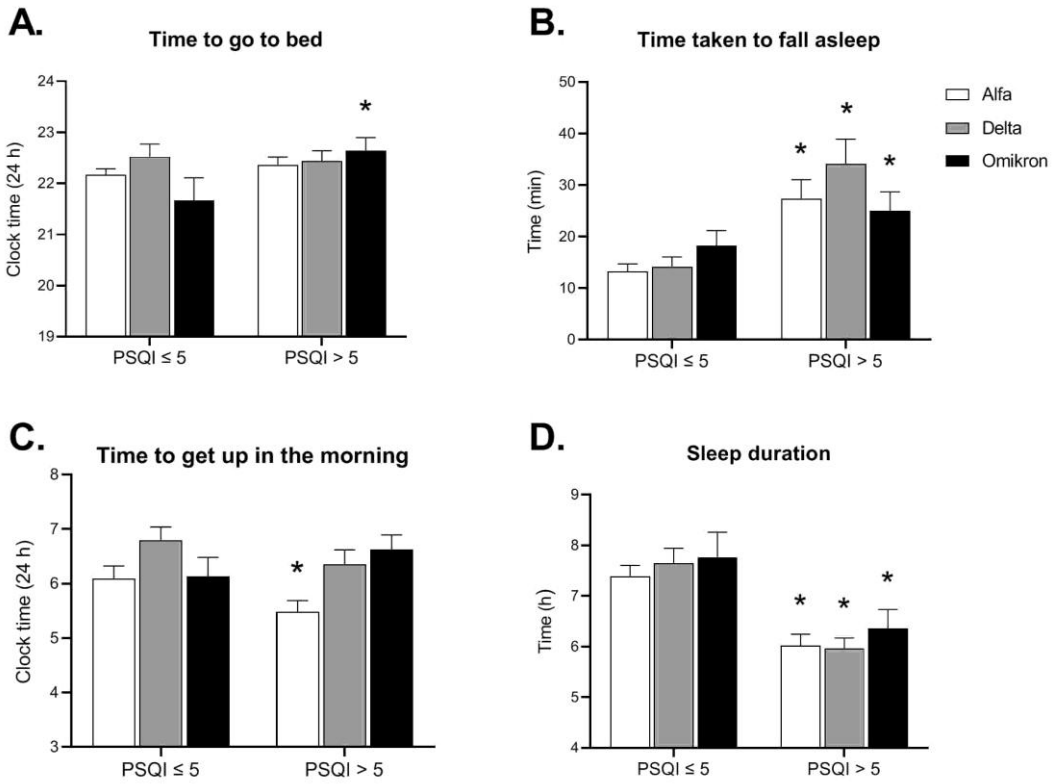

Fig. 10. Sleep-wake rhythm parameters of long COVID patients during the COVID-19 epidemic waves caused by the Alpha, Delta, and Omicron variants. The figure separately shows patient groups with adequate (PSQI ≤ 5) and inadequate sleep quality (PSQI > 5) for each variant. $p < 0.05$ vs. PSQI ≤ 5 (Percze AR, Bardóczi AB, Nagy A, et al. Post-COVID-19 symptoms and sleep-wake abnormalities during the COVID-19 pandemic waves in Hungary. Orv. Hetil. 2025;05. 166(21):817-825.)

5. Discussion

Analysis of sleepiness, fatigue and sleep quality in COVID-19 patients

Recent evidence has shown that various complaints could persist long after the SARS-CoV-2 infection, but the virus variant-specific patterns of these symptoms are not known. This retrospective study provides novel information on these "long COVID fenotypes" in connection with 3 variants, namely Alpha, Delta, and Omicron. One of the main findings of the study is that, despite their differences in their clinical course of acute infection, these VOCs share important similarities.

The Alpha variant was first detected worldwide in September 2020. Due to mutations that increased its transmissibility and ability to evade the immune system, it led to a significant rise in COVID-19 cases and hospitalizations, and posed a higher risk of severe disease and mortality compared to the original strain (135). The Delta variant was characterized by high viral loads and a longer infectious period, changes attributed to mutations that increased the replication rate of SARS-CoV-2. Together with additional mutations that enhanced its affinity for the ACE2 receptor, these alterations resulted in increased transmissibility and disease severity, leading to more frequent hospitalizations, intensive care admissions, and higher mortality (136). The Omicron variant, due to its unusually high number of unique mutations, spread more rapidly and caused more reinfections. However, compared to the Delta variant, it was generally less severe in terms of hospitalizations and mortality (137).

Our study focused on the VOCs from the three consecutive waves of the COVID-19 pandemic. To our knowledge, these represent the first Hungarian data on long-term complications associated with COVID-19, such as fatigue and sleep disturbances. Furthermore, this is the first study to assess the role of three different VOCs in relation to long COVID symptoms.

Our investigations, based both on structured anamnesis interviews and data from the PSQI questionnaire, confirmed the frequent occurrence of post-COVID-19 sleep disturbances (132), a finding that has also been recently corroborated by other studies (138).

Our research approach was supported by the clear differences observed in the clinical presentation of acute infections caused by different VOCs (139) and the

presumed diversity in virus-host interactions. We tested our hypothesis in long COVID patients who were highly similar in terms of demographic and clinical characteristics. We found notable similarities among the long-term effects of the three VOCs regarding both fatigue and sleep quality. This finding was further reinforced by a comparative analysis of the PSQI component scores, which assess specific aspects of sleep, revealing similar long-term responses to viral infection across all examined dimensions of sleep in all three pandemic waves. Based on these observations - given the consistent long-term effects on both fatigue and sleep quality - our data may even support the existence of a common virus-host mechanistic pathway underlying chronic fatigue and sleep disturbances in long COVID.

In our study, poor sleep quality was common (> 60%) among long COVID patients, consistent with findings from other recent studies (140). Multiple factors may contribute to the pathogenesis of sleep disturbances associated with long COVID (90). SARS-CoV-2 can infect the central nervous system, inducing neuroinflammation that may lead to long-term detrimental effects. Beyond direct viral infection, other proposed pathological processes contributing to sleep disturbances include cerebrovascular changes, infection-related damage triggered by autoimmune processes, and inflammation-mediated central nervous system injury. The latter may even function as a self-perpetuating mechanism, creating a vicious cycle, as sleep disorders can induce neuroinflammation, disrupt the blood-brain barrier, and facilitate the entry of antigens and inflammatory mediators into the brain (141).

In addition to the pathomechanisms of viral infection, reductions in sleep quantity and quality have been associated with stress, anxiety, and depression induced by the COVID-19 pandemic (142). The negative societal consequences of the COVID-19 pandemic primarily stemmed from the overburdening of healthcare systems and the strict public health measures implemented to contain the pandemic (143, 144). During the pandemic, fear of infection, illness, and severe outcomes became a part of daily life. In addition to travel restrictions, measures such as social distancing and strict quarantine rules were implemented to control the spread of the disease. During periods of social isolation, reduced mobility and limited social interactions, concerns over income loss and dwindling supplies, as well as uncertainty regarding the duration of voluntary quarantine, further negatively impacted the mental health of the population (103, 107).

In addition to the consequences of acute infection and environmental factors, persistent post-COVID-19 symptoms also impair sleep quality. However, few studies have investigated which specific symptoms and SARS-CoV-2 variants are responsible for poor sleep quality.

One of the main findings of the study is that, despite differences in the clinical course of acute infection, these VOCs also exhibit important similarities in connection with their long term consequences (i.e. fatigue and poor sleep quality). Our findings highlight the importance of concerted efforts to manage both fatigue and sleep disturbances in long COVID patient care. This multifaceted approach should be followed in all cases infected with either VOCs of SARS-CoV-2.

Analysis of acute/post-infection symptoms and circadian sleep-wake rhythm in COVID-19 patients with post-COVID sequelae

In addition to transmissibility, clinical symptoms, and disease severity, the type of SARS-CoV-2 variant also influences the long-term consequences of COVID-19. Sleep disturbances - characteristic symptoms during SARS-CoV-2 infection, affecting nearly two-thirds of patients - are among the most common post-COVID-19 outcomes. Our retrospective study, based on data from the COVID-19 epidemic waves in Hungary, highlights the variant-dependent occurrence of post-COVID-19 symptoms and sleep-wake disturbances, as well as their interrelationships. Understanding the precise link between post-COVID-19 complications and specific SARS-CoV-2 variants is of primary importance, as it may contribute to the development of effective treatment strategies for managing the disease.

Although our study also confirms that fatigue is clearly the most common symptom across all three variants, among other post-COVID-19 manifestations, the incidence of shortness of breath decreased, while the occurrence of cough and palpitations increased over successive COVID-19 waves. The differences we observed between the Alpha, Delta, and Omicron variants support the view that post-COVID-19 consequences should not be considered a uniform condition, but rather a disease pattern that varies across pandemic waves due to the distinct characteristics of each variant.

One of the earliest observations during the COVID-19 pandemic was the frequently prolonged sleep disturbances among patients recovering from SARS-CoV-2 infection (101, 140). Our previous studies confirmed the common occurrence of post-COVID-19 sleep disturbances (see above) (140). Poor sleep quality has been shown to be associated with delayed return to work, reduced work performance, an increased risk of psychiatric disorders, and higher healthcare costs. Despite numerous hypotheses, the pathogenesis of post-COVID-19 sleep disturbances remains unclear (90).

Our study revealed that post-COVID-19 symptoms differ significantly between viral variants in patients experiencing poor sleep quality. While fatigue, cough, and shortness of breath were almost universally more common among those with poor sleep, fatigue was also observed in patients with adequate sleep quality in the case of the Omicron variant. The most notable difference between variants concerned palpitations: their occurrence was low with the Alpha variant, high with the Delta variant when sleep quality was poor, and consistently high with the Omicron variant regardless of sleep quality. For the latter variant, the frequency of palpitations as a post-COVID-19 symptom can approach - or even exceed - its occurrence during acute COVID-19 in patients with poor sleep.

Post-COVID sleep disturbances represent a serious health concern for patients recovering from infection (145, 146). The most common form is insomnia, characterized by difficulty falling asleep, frequent nighttime awakenings, and non-restorative sleep. In contrast to typical insomnia sufferers, many patients also report daytime sleepiness and an increased need for sleep. Other notable sleep problems include worsening of obstructive sleep apnea, transient episodes of restless legs syndrome, and the occurrence of nightmares (112, 147, 148). Due to disruptions in the sleep–wake rhythm, many individuals also experience shifted sleep patterns, such as delayed sleep onset and late awakening. The sleep-wake disturbances observed in our study resemble, in several respects, those seen in insomnia and delayed sleep phase syndrome, yet the specific features associated with each SARS-CoV-2 variant highlight the heterogeneity of post-COVID sleep disturbances. Supporting this, prolonged sleep latency and shorter total sleep time - typical of insomnia - were observed across all three variants; however, early awakening, another hallmark of insomnia, was noted only in

the Alpha variant, whereas delayed bedtime, indicative of delayed sleep phase syndrome, was observed exclusively in the Omicron variant.

The main limitations of our study include its retrospective, single-center design and the absence of a healthy control group. The type, dose, and schedule of SARS-CoV-2 vaccination may also have influenced our results, and therefore these findings should be interpreted with caution. In addition, we did not analyze infection severity or the treatments administered. Another limitation is that the associations between the examined characteristics and viral variants are based on data from COVID-19 patients infected during epidemic waves caused by specific variants, without individual viral variant typing. Consequently, it cannot be excluded with certainty that some cases during a given wave were infected with other viral variants. Furthermore, due to the unpredictability of infection occurrence and the retrospective nature of the study, patients' pre-infection sleep quality was not assessed, making it impossible to directly compare sleep characteristics before and after infection. Finally, it should be noted that our study strategy focused on comparing post-COVID-19 patients with adequate and poor sleep quality in terms of sleep-wake rhythm, and did not include additional control groups, such as uninfected individuals, asymptomatic post-infection subjects, or patients who fully recovered from COVID-19 without symptoms.

6. Conclusions

Recognizing and appropriately managing persistent sleep disturbances and other post-COVID-19 complications is of fundamental importance to patients and constitutes a shared responsibility among multiple specialties, including pulmonology, sleep medicine, rehabilitation, and neurology. Our research highlights the variability of post-COVID-19 symptoms observed across successive epidemic waves, reflecting genetic changes in SARS-CoV-2 and the emergence of new variants. Despite ongoing changes in SARS-CoV-2, sleep disturbance remains one of the most common post-COVID-19 complications and requires heightened clinical attention and appropriate diagnostic and management strategies. A more precise understanding of the relationships between specific SARS-CoV-2 variants and the post-COVID-19 complications and sleep-wake disorders they induce may help improve treatment strategies.

In our effort to investigate how SARS-CoV-2 variant type influences long-term sequelae, we conducted retrospective analyses of sleep-related data from COVID-19 patients across the three major epidemic waves. These analyses revealed the following novel findings:

1. Self-reported questionnaires indicated higher (worse) scores for fatigue, daytime sleepiness, and sleep quality in patients with post-COVID-19 symptoms across the three epidemic waves. However, only fatigue and sleep quality - not daytime sleepiness - exceeded the normal range.
2. Based on PSQI component scores, a more detailed analysis of sleep quality in long COVID patients revealed no significant differences across the three COVID-19 epidemic waves.
3. Across the three successive epidemic waves, fatigue remained the most common post-COVID-19 symptom for all three variants, while the prevalence of dyspnea decreased and that of cough and palpitations increased.
4. The prevalence of post-COVID-19 symptoms was generally higher among poor sleepers, but considerable heterogeneity was observed across the three COVID-19 waves. Fatigue was more frequent in poor sleepers for the Alpha and Delta variants and remained common ($\geq 60\%$) for the Omicron variant, regardless of sleep quality. Cough and dyspnea were more frequent in poor sleepers across all three variants. Palpitation was rare ($< 25\%$) in the Alpha variant, more frequent (50%) among poor

sleepers in the Delta variant, and consistently high (≥ 50%) in the Omicron variant, irrespective of sleep quality.

5. Our analysis of sleep-wake rhythms in long COVID patients revealed variant-specific changes associated with poor sleep quality, including delayed bedtime in the Omicron variant, earlier wake-up time in the Alpha variant, and prolonged sleep latency with reduced sleep duration across all three variants.

Our studies demonstrate that, in addition to fatigue, sleep problems can remain an important burden for long COVID patients. Since sleep quality and circadian rhythmicity have a profound role in physiological and mental wellbeing, these findings highlight the importance of sleep quality assessments and a multi-disciplinary approach in long COVID patient care. Furthermore, despite the reported differences in the course of acute disease caused by various VOCs, equally negative long-term effects should be expected for either Alpha, Delta, or Omicron variants of SARS-CoV-2 on fatigue and sleep quality. However, further research is needed to identify the impact of vaccination on fatigue and sleep disturbances in long COVID patients. Our studies also confirm the variant-dependent heterogeneity of post-COVID-19 symptoms and sleep-wake disturbances. Understanding their association with post-COVID-19 complications may help elucidate the significance of genetic changes in SARS-CoV-2.

7. Summary

Sleep disturbance is one of the most common long-term negative health consequences following acute COVID-19. Sleep disorders, along with frequently associated chronic fatigue, may contribute to further complications, including metabolic and cardiovascular diseases, psychological and concentration disorders, reduced immune response, and negatively affect health-related quality of life, physical activity, and mental health.

Pulmonologists - often involved due to respiratory long COVID complications - play a key role in recognizing and managing sleep problems, which, due to their high prevalence, cannot be addressed solely within the framework of sleep medicine. Challenges include the wide variety of sleep disorders, their complex mechanisms, and the lack of specific treatments for long COVID complications. The most important aspects of practical care, besides early recognition, are identifying and treating potential organic causes, adhering to general recommendations for the prevention and treatment of sleep disorders, and applying therapeutic methods tailored to the specific type of sleep disturbance. Decreased physical endurance, impaired respiratory mechanics, and muscle loss due to the disease can be improved through complex pulmonary rehabilitation, which can also positively impact patients' sleep quality.

Our studies indicate that COVID-19 infection and sleep disorders are closely interrelated, and therefore, the care of affected patients, as well as the restoration of their quality of life and work capacity, is a key responsibility not only of sleep medicine but also of several other medical specialties. Our research confirms the variant-dependent heterogeneity of post-COVID-19 symptoms and sleep-wake disturbances. Understanding the associations with post-COVID-19 complications may also help to uncover the significance of genetic changes in SARS-CoV-2.

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9. Bibliography of the candidate's publications

9.1. Articles

1. Percze AR, Nagy A, Polivka L, Barczi E, Czaller I, Kovats Zs, Varga JT, H. Ballai J, Muller V, Horvath G: Fatigue, sleepiness and sleep quality are SARS-CoV-2 variant independent in patients with long COVID symptoms; Inflammopharmacology „Special issue – Long Covid"; IPHM-D-23-00182R0; https://doi.org/10.1007/s10787-023-01190-4
   IF: 4,6 (Q1)
2. Percze AR, Bardoczi AB, Nagy A, Horvath G, Varga JT, Muller V, Horvath G: Long COVID Sleep Disorders in Pulmonology Practice; Medicina Thoracalis 2023; 77(2): 45-53
3. Percze AR, Bardoczi AB, Nagy A, Vasas Sz, Varga JT, Muller V, Horvath G: Post-COVID−19 symptoms and sleep-wake abnormalities during the COVID−19 pandemic waves in Hungary; Orvosi Hetilap, 2025; 166(21): 817–825.
   IF: 0,9 (Q4)

9.2. Citable abstracts

1. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; Rector's Scientific Competition Essay, 2021
2. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; Medical Education (Orvosképzés) 2022, Volume XCVII, Issue 1; 1: 1–336
3. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Post-COVID Sleep Disorders: Correlations with Persistent Respiratory Disturbances and Functional Status; Medicina Thoracalis, Volume 75, Issue 3, 2022, Abstract 85. BI/2
4. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; Medical Education (Orvosképzés) 2023, Volume XCVIII, Issue 2; 2: 345–700

9.3. Congress presentations

1. Horvath G, Percze AR, Kovats Zs, Varga JT, Muller V: Sleep Disorders Related to COVID; 25th Meeting of the Cardiopulmonary Section of the Hungarian Society of Pulmonology and Thoracic Surgery (MKT-MTT), Gödöllő, September 24–25, 2021
2. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; Scientific Students' Conference (TDK), February 9–11, 2022
3. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Post-COVID Sleep Disorders: Correlations with Persistent Respiratory Disturbances and Functional Status; 62nd Congress of the Hungarian Pulmonological Society (MTT), Győr, May 18–21, 2022
4. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; 13th Congress of the Hungarian Society of Sleep Diagnostics and Therapy (MATT), Siófok, September 9–10, 2022
5. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Post-COVID Sleep Disorders in Pulmonology Practice; 13th Congress of the Hungarian Society of Sleep Diagnostics and Therapy (MATT), Siófok, September 9–10, 2022
6. Horvath G, Percze AR, Nagy A, Polivka L, Kovats Zs, Varga JT, Muller V: Sleep Quality in Long COVID-19 Patients: Relation to Symptoms, Pulmonary Function, and Functional Capacity; European Respiratory Society (ERS) International Congress, Prague, Czech Republic, April 20–22, 2023
7. Percze AR, Kovats Zs, Varga JT, Muller V, Horvath G: Relationships Between Pulmonological Functional Status and Sleep Quality in Post-COVID Patients; 36th National Scientific Students' Conference (OTDK), April 18–21, 2023
8. Percze AR, Nagy A, Polivka L, Horvath G, Bardoczi AB, Czaller I, Kováts Zs, Varga JT, Muller V, Horvath G: Fatigue, Sleepiness, and Sleep Quality in Long-COVID Syndrome Patients: A Comparative Study of the Role of the Alpha, Delta, and Omicron SARS-CoV-2 Variants; November 17–18, 2023

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