Retrospective analysis of post-COVID-19 symptoms in hospitalized patients, comparing the different SARS-COV-2-variants regarding headache

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RETROSPECTIVE ANALYSIS OF POST-COVID-19 SYMPTOMS IN HOSPITALIZED PATIENTS, COMPARING THE DIFFERENT SARS-COV-2-VARIANTS REGARDING HEADACHE

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For all that happened in the past and all that is coming in the future, never forget:

Yesterday is history, tomorrow is a mystery, but today is a gift, that is why it's called the present.

List of Abbreviations:

SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
WHO	– World Health Organization
bat-SL-CoV	– bat SARS-like coronavirus
MERS-CoV	– middle east respiratory syndrome coronavirus
ACE2	– angiotensin converting enzyme 2
TMPRSS2	– transmembrane protease serine 2
RNA	– ribonucleic acid
vWF	– von Willebrand factor
CRP	– c-reactive protein
IL-6, IL-7	– interleukin 6, interleukin 7
TNF-α	– tumor necrosis factor-alpha
CCL2, CCL3	– chemokine (C-C motif) ligand 2, chemokine (C-C motif) ligand 3
DIC	– disseminated intravascular coagulation
MicroCLOTS	– microvascular COVID-19 lung vessel obstructive thrombo-inflammatory syndrome
ANGII	– angiotensin 2
AT1R	– angiotensin type I receptor
PE	– pulmonary embolism
R0	– basic reproduction number
VOC	– SARS-CoV-2 variant of concern
CDC	– Center for Disease Control and Prevention
SpO2	– oxygen saturation
PaO_2/FiO2	– ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
NVSS	– National Vital Statistics System
COPD	– chronic obstructive pulmonary disease
BMI	– body mass index
NP specimen	– nasopharynx specimen
OP specimen	– oropharynx specimen
NAAT	– nucleic acid amplification technology
RT-PCR	– reverse transcriptase-polymerase chain reaction
RKI	– Robert Koch Institute

ELISA	– enzyme linked immunosorbent assay
CBC	– complete blood count
LDH	– lactate dehydrogenase
MAS	– macrophage activation syndrome
WBC	– white blood cell count
BNP	– brain natriuretic peptide
BMP	– basic metabolic panel
AST	– aspartate transaminase
ALT	– alanine transaminase
CT	– computed tomography
ECMO	– extracorporeal membrane oxygenation
JAK	– janus kinase
PTSD	– post-traumatic stress disorder
ARDS	– acute respiratory distress syndrome
POTS	– postural tachycardia syndrome
MIS	– multisystem inflammatory syndrome
ME/CFS	– Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
ESR	– erythrocyte sedimentation rate
AKI	– acute kidney injury
mRNA	– messenger ribonucleic acid
VOI	– variant of interest
VUM	– variant under monitoring
TTH	– tension-type headache
NSAIDs	– non-steroidal anti-inflammatory drugs
CW	– calendar week
ICU	– intensive care unit
IRB	– Institutional Review Board
SD	– standard deviation

1. INTRODUCTION

1.1 SARS-CoV-2

1.1.1 Time and History

The COVID-19 pandemic is an ongoing global health crisis that has affected nearly every corner of the world. The pandemic was caused by a novel coronavirus, SARS-CoV-2, which was first identified in Wuhan, China, in December 2019. Since then, the virus has spread rapidly throughout the world, with millions of confirmed cases and thousands of deaths (1, 2). The virus is primarily spread through respiratory droplets when an infected person coughs, sneezes, or talks, but can also be transmitted through contact with contaminated surfaces (3). COVID-19 symptoms can range from mild to severe and can include fever, cough, difficulty breathing, and loss of taste or smell (4).

SARS-CoV-2 started at the end of 2019 and became public at the beginning of the year 2020 with its spreading in the Chinese city of Wuhan. On December 12th 2019., a group of patients in Hubei, China, experienced symptoms of atypical pneumonia, that did not respond well to standardized treatments. On the 31st of December, the WHO was informed about a new pneumonia with an unknown etiology and a connection to the Huanan Seafood Wholesale Market in Wuhan. After over 40 positive cases, the WHO identified the causative agent as a novel coronavirus on the 7th of January 2021. After further multiple new positive cases in China, Thailand, Japan, and the Republic of Korea, combined with the total lockdown of Wuhan on the 23rd of January. the first laboratory-confirmed case of SARS-CoV-19 was reported in the U.S. on the 20th of January. Until January the 30th 2020., all positive cases were travel related. However, on that day the CDC confirmed the first person-to-person transmission in Illinois, USA. While the virus spread rapidly through Asia and was distributed further in the USA, on the 23rd of February, Italy became a new COVID hotspot and got placed under lockdown. On the 11th of March 2020, COVID-19 was officially declared a pandemic by the WHO, with over 118.000 cases in 114 countries and 4.291 deaths (1).

Since then, the world experienced multiple lockdowns, vaccinations, new COVID waves, and different policies on how to manage the virus, while the disease is still being declared as a pandemic, with as of today, 24th of May 2023, 766.895.075 confirmed cases and 6.935.889 deaths (2). In response to the pandemic, many countries have implemented measures such as social distancing and the use of masks to slow the spread of the virus. Vaccines have also been developed, with the goal of herd immunity and ending the pandemic (5, 6).
Despite these efforts, the pandemic had a significant impact on the global population with far-reaching economic, social, and psychological effects on individuals worldwide (7).

1.1.2 Etiology

SARS-CoV-2, also known as Severe Acute Respiratory Syndrome Coronavirus 2, is a type of coronavirus known as a β-coronavirus first discovered in bronchoalveolar lavage samples from patients in Wuhan, China. With its first discovery on the Huanan Seafood Market, trading with live and dead animals, a zoonotic origin of the virus is suggested, however still not confirmed (8). Furthermore, the virus has a greater similarity to the SARS-like coronaviruses from bats (bat-SL-CoVZC45 and bat-SL-CoVZXC21) (88% identity), than to other coronaviridae like SARS-CoV (79%) or MERS-CoV (50%) supporting the zoonotic theory (9).

SARS-Cov-2 is characterized as an enveloped, non-segmented, positive-sense, single-stranded RNA virus, being part of the Sarbecovirus subgenus of the Coronaviridae family (10, 8). Its viral genome contains several structural and nonstructural components. Within the four structural proteins, the spike protein plays a key role, facilitating viral entry and initiating the infection, by attaching to the ACE2 receptor on the surface of host cells. The envelope and membrane proteins form the viral envelope, and the nucleocapsid protein is responsible for packaging of the genome into a helical ribonucleocapsid structure (10). Additionally, the viral genome of SARS-CoV-2 encodes 16 non-structural proteins. These proteins form the replicase–transcriptase complex, responsible for viral replication and transcription processes (11). Combined, the interplay of structural and non-structural proteins is crucial in the lifecycle of SARS-CoV-2, contributing to its ability to infect and replicate within host cells (Figure 1.).

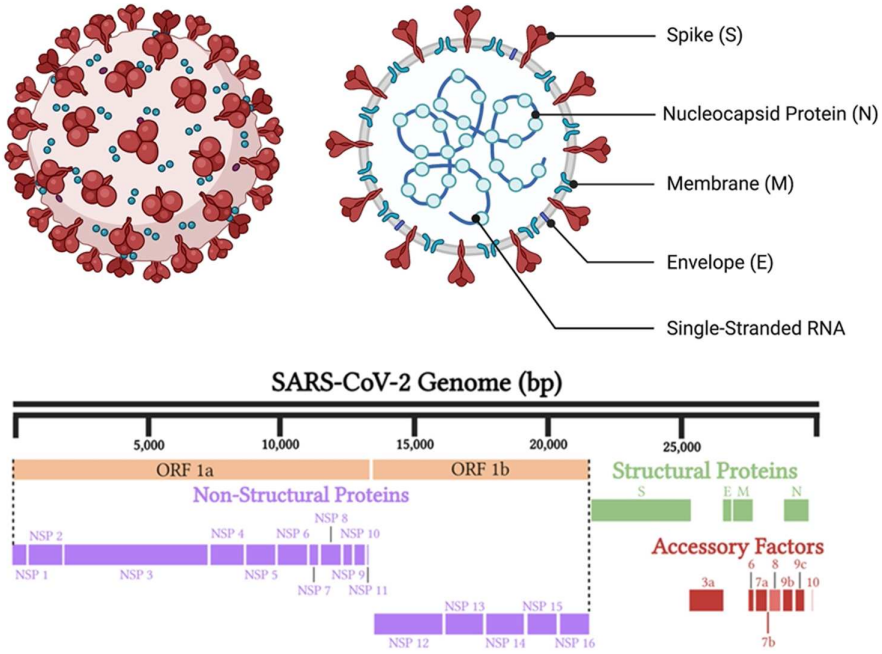

Figure 1. SARS-CoV-2 structure

Source: SARS-CoV-2 structure. | European Journal of Human Genetics. [cited 2023 Jul 6]; Available from: https://www.nature.com/articles/s41431-022-01108-8/figures/1

1.1.3 Pathophysiology (Intracellular)

The invasion of host cells by SARS-CoV-2 begins with the initial step of spike protein binding from the virus surface, to the membrane protein angiotensin-converting enzyme 2 (ACE2). With this interaction, the affiliation of the virus to the target cell is facilitated. After the attachment, a host protease called transmembrane protease serine 2 (TMPRSS2) activates the viral spike protein and primes it for viral entry into the cellular host.

During membrane fusion of the viral envelope and host cell, the viral genetic material enters the cytoplasm in the form of RNA. With the release of RNA into the invaded cell, the replication cycle begins and virally induced enzymes, such as RNA polymerase or proteases, play a key role in releasing and replicating the viral components. These components accumulate and form new viruses, which are then enclosed in endosomes. Via the process of exocytosis, the endosomes are finally released from the infected cell. Overall, the invasion and replication cycle of SARS-CoV-2 involves the binding of the spike protein to ACE2, activation by TMPRSS2, membrane fusion, release of viral RNA, replication of viral components, assembly of new viruses, and eventual release of these viruses from the infected host cell (Figure 2.) (10).

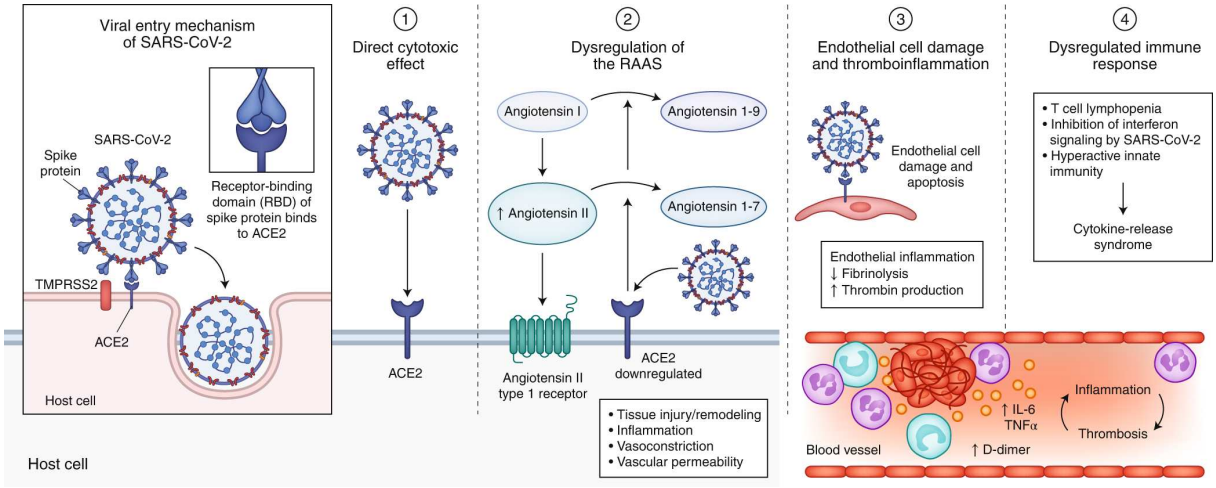

Figure 2. Pathophysiology of extrapulmonary manifestations of COVID
Source: Fig. 1: SARS-CoV-2 structure. | European Journal of Human Genetics. [cited 2023 Jul 6]; Available from: https://www.nature.com/articles/s41431-022-01108-8/figures/1

1.1.4 Pathophysiology (Extracellular)

Apart from intracellular mechanisms, there are also extracellular effects caused by SARS-CoV-2 (Figure 2.). Once the virus is released into the body, a hypercoagulable state develops, characterized by elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor. Although the pathophysiology is not yet fully understood, there is a hypothesis that hypercoagulability develops through two mechanisms.

On one hand, the virus itself is capable of activating the coagulation cascade. On the other hand, the body's immune response triggers a hyper-thrombotic state via cytokine storm, complement activation, and endothelial inflammation. Viral binding to the ACE2 receptor in pulmonary alveoli triggers an inflammatory response, causing elevation of cytokines, C-reactive protein (CRP), lactate dehydrogenase, and ferritin.

The excessive release of cytokines, such as interleukin-6 (IL-6), interleukin-7 (IL-7), soluble interleukin-2 receptor, tumor necrosis factor-alpha (TNF-α), and chemokines (CCL2, CCL3), leads to the activation of neutrophils, monocytes, and the endothelium. This activation contributes to the development of a hypercoagulable state. There is also a correlation between elevated levels of Interleukin-6 and increased fibrinogen levels, which further supports the hypothesis of hypercoagulability.

Furthermore, a localized coagulopathy can be observed in the pulmonary vasculature, presenting a disseminated intravascular coagulation (DIC)-like pattern. This pathophysiological mechanism is suggested to be called "microvascular COVID-19 lung vessel obstructive thrombo-inflammatory syndrome" (MicroCLOTS).

The endothelial dysfunction, characterized by elevated levels of vWF and factor VIII, results from direct damage and infection of endothelial cells. Additionally, it can be attributed to hyperactivation by the complement system and the release of inflammatory cytokines.

As the virus binds to ACE2 for cell entry, internalization, and shedding of ACE2 occur, resulting in a decrease in the number of ACE2 receptors. Normally, ACE2 is responsible for inactivating angiotensin II (ANGII). However, in the case of COVID-19, impaired inactivation leads to an elevation of ANGII levels. The increased ANGII binds to the angiotensin type I receptor (AT1R), which contributes to lung injury and subsequently leads to the release of elevated levels of IL-6, further triggering a cytokine storm. In addition to viral or immune-related pathophysiology, critically ill patients are at increased risk of thromboembolism. This risk is attributed to factors such as prolonged bed rest, mechanical ventilation, deficiencies in nutrition, or the presence of central venous accesses (Summary in Figure 2.).

The hypercoagulable state often manifests as venous thromboembolism, primarily in the form of pulmonary embolism (PE). Additionally, thrombotic microangiopathy, stroke, myocardial infarction, and additional end-organ damage due to hypercoagulation are also possible (12).

1.1.5 Transmission

Since the confirmed person-to-person transmission of SARS-CoV-19 in Illinois, on the 30th of January 2020, the known primary route of transmission is via exposure to respiratory fluids, which can occur in two different ways (1, 13).

Dissemination is possible in the form of droplet transmission. This happens when an infected individual releases respiratory droplet by coughing, sneezing, talking, or breathing heavily. Because these droplets are relatively large, they quickly fall to the ground or onto surfaces within a short distance of about 3 – 6 feet from the infectious source.

With airborne transmission, smaller aerosol particles containing the virus remain suspended in the air for longer periods. These aerosols can be directly inhaled by others. It is important to note that airborne transmission is more likely to occur with prolonged exposure to aerosols in poorly ventilated areas and enclosed spaces. The concentration of aerosol particles tends to be highest within a close range of 3 – 6 feet from the infectious source. These small aerosol particles can linger in the air for minutes to hours, potentially increasing the risk of transmission in crowded or confined spaces.

Additionally, to droplets and aerosols as primary transmission, the direct contact of mucous membranes (for example eyes, nose, or mouth) with respiratory droplets of an infected individual can also result in positive transmission.

During the pandemic, the transmission over contaminated surfaces (fornite transmission), created a risk factor for infection in public facilities. However, this mechanism of dissemination is considered less significant compared to the respiratory transmission of COVID-19. Still, well-practiced hand hygiene and the regular disinfection of frequently touched surfaces act as important preventive measures against infection (13).

1.1.6 Basic Reproduction

In understanding the different modes of transmission, the question arises of how the virus could spread so rapidly throughout the world? In order to answer, one must take a closer look at the number of secondary infections caused by a single infected individual, which can be measured by the basic reproduction number (R0). It is important to note, that R0 changed with the different COVID variants. With the 2019 strain of SARS-CoV-2 (2019-nCoV), the R0 ranged from 2.24 – 3.58, meaning that one infected person transmitted the virus to 2.24 – 3.58 other individuals, on average (14).

The newer virus variants, presented with a higher R0 compared to 2019-nCoV and were characterized as SARS-CoV-2 variants of concern (VOC).

The WHO defines VOC as variants with evidence of increased transmissibility, decreased treatment or vaccine effectiveness, diagnostic detection failure, reduced antibody neutralization from previous infections or vaccinations, and evidence of a more severe disease regarding hospitalization or deaths (15).

While the Delta variant (B.1.617.2) presented with an already increased transmissibility, as shown by the average R0 of 5.08, the Omicron variant (B.1.1.529) exhibited with an even greater average R0 of 9.5 (16,17). This means that the newer variants have the potential to spread more easily and rapidly within the population.

Several factors influence the basic reproduction number and the spread of COVID-19. Firstly, there is the duration of contagiousness, which typically starts at a mean of 2 days before the onset of symptoms (18). Rarely, do patients continue to be contagious after more than 10 days from symptom onset (19). The longer the contagiousness, the greater the risk of infecting another individual. Virus mutations and immune evading mechanisms further have a direct effect on the effectiveness of vaccines and the spreading of the virus (17).

The rate of close contact between infected and uninfected individuals also presents an important factor affecting the R0. Hereby, modes of transmission, such as respiratory droplets or aerosols, play a key role in determining the risk of infection spreading (13).

Efforts to reduce the contact rate, such as practicing social distancing and implementing quarantine measures, aim to lower the R0 by reducing the opportunities for the virus to spread from person to person (20). Understanding and monitoring the R0 is crucial for assessing the potential impact of the disease and informing public health strategies to control its spread. It is important to note that the R0 may vary over time and in different populations.

1.1.7 Clinical Presentation

With SARS-CoV-19 primarily exerting direct cytopathic effects on the alveolar epithelium, the disease clinically presents with symptoms associated with the respiratory tract (21). The CDC states, that after an incubation period of 2 to 14 days, with an average of 4 to 5 days, 97,5% will have symptoms within 11.5 days (22, 23). Affected individuals present with a combination of fever, cough, shortness of breath, and fatigue. Additionally, there might also be a sore throat or rhinitis present, and the loss of smell and/or taste can occur. However, the virus's presentation is not limited to the respiratory tract. Headache, myalgia, or gastrointestinal symptoms such as diarrhea, loss of appetite, or vomiting can also occur (22). It is important to note that, the majority of affected individuals, are asymptomatic. Furthermore, virus variants like Delta or Omicron have displayed a milder clinical presentation.

The presentation of COVID varies from patient to patient, and might also present with atypical or extrapulmonary symptoms alone (24). Thereby, it is significant to mention, that only the most common symptoms are mentioned here. The presentation also differs between age groups. Most children experience asymptomatic or mild disease, while in older individuals, delirium with weakness, reduced mobility or falls, and glycemic changes can occur (22, 25).

1.1.8 Severity

Regarding the severity assessment of SARS-CoV-19, the CDC grouped the disease expression into five categories: asymptomatic or pre-symptomatic infection, mild illness, moderate illness, severe illness, and critical illness. In an asymptomatic patient, or one, currently without symptoms, who develops a clinical manifestation later (pre-symptomatic), the affected individual presents with a positive antigen test but without any clinical signs. In the case of mild illness, people show signs of COVID-19 but without dyspnea, hypoxemia, or abnormal chest imaging. If there are signs of viral pneumonia on either clinical assessment or imaging but still no hypoxemia with oxygen saturation (SpO_2) $\geq$ 94% on room air at sea level, the CDC categorizes this presentation as moderate illness.

However, if the SpO_2 is below 94%, with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) less than 300mmHg and a respiratory rate of over 30 breaths per minute, we have a state of severe illness. In the worst case of a critical illness, the individual presents with respiratory failure, septic shock, or multi-organ dysfunction (22).

1.1.9 Risk Factors for Severe COVID Progression

To classify the disease severity, the CDC also highlights certain risk factors for developing a severe progression of COVID-19 with age above 65 years, being the strongest factor. With the data of the National Vital Statistics System (NVSS), the risk of developing a severe disease compared to 18 – 29 year old individuals, is 25 times higher between 50 – 64 years, 60 times increased in 65 – 74 years, 140 times more in the age between 75, and 84 years and 340 times greater with an age above 85 years (26).

Furthermore, race and ethnicity also affect the risk of a severe illness progression. People from racial and ethnic minority groups are at greater risk to be hospitalized, admitted to the intensive care unit, or dying at a younger age due to COVID-19 (27).

Regarding medical conditions, it is not only the presence of a specific condition that impacts the risk of severe progression but also the number of medical conditions an individual presents with. The greater the number of medical conditions, the higher the risk of severity.

Among hospitalized patients, the risk of death due to SARS-CoV-19 increases by 1.5 with one condition, by 2.6 with 2 – 5 conditions, by 3.3 with 6 – 10 conditions, and by 3.8 with 10 or more conditions. Conditions, which increase the severity risk include cardiovascular disorders (heart failure, coronary artery disease or cardiomyopathies), chronic lung diseases (asthma, bronchiectasis, COPD, pulmonary embolism or -hypertension, and interstitial lung diseases), chronic kidney disease, chronic liver diseases (cirrhosis, alcoholic/non-alcoholic fatty liver disease, autoimmune hepatitis), diabetes (type 1 and 2) cerebrovascular disorders, mental health conditions and immunodeficiencies to name a few.

Last but not least, also lifestyle plays a role in increasing the risk. These include obesity with a BMI greater than 30 or above the 95th percentile in children, physical inactivity, smoking, or recent/ongoing pregnancy (26).

1.1.10 Diagnosis

Diagnostic testing was considered for either individuals with COVID symptoms, people with high-risk exposures, screening purposes, or ending of isolation. It is important to note that testing recommendations changed with the progression of the pandemic and differed also in between countries and populations. The standard diagnostic approach to COVID-19 involves the widespread use of diagnostic testing via specimens from the upper respiratory tract.
The preferred method of sample acquisition stems from the nasopharynx (NP specimen), while additional options involve collections from the oropharynx (OP specimen), the nasal mid-turbinate location or its anterior nares, and from saliva (28).

The combination of NP- and OP specimens in a single tube maximizes the sensitivity of the analysis. In the case of an intubated patient with negative assessment from the upper respiratory tract but with suspected COVID pneumonia, a specimen gathered from the lower respiratory tract via aspirate or bronchoalveolar lavage is recommended (29).

COVID-19 Tests used for diagnostic confirmation are composed of serological diagnosis, involving nucleic acid amplification- (NAAT, PCR-based) or antigen testing, in addition to serological testing, which is not routinely recommended.

NAAT, RT-PCR bears the gold standard for the detection of an active SARS-CoV-19 infection, providing high sensitivity and specificity for COVID (28). Viral RNA is transcribed into complementary DNA which gets amplified, to detect viral genetic material (30).

It can take up to five days post-exposure for RT-PCR to be able to detect the virus. The downside of this method is the longer turnaround time of 2 hours compared to the antigen testing with almost immediate results within 15 – 30 minutes and lower required costs. Although less sensitive, the antigen test became the most commonly used method of diagnosis due to its wide availability, faster results, and the option, to be carried out by non-medically educated individuals (28). During the procedure, the virus gets diagnosed by direct detection of its protein fragment antigens (30). Additionally, the antigen approach has a similar specificity compared to the PCR diagnosis (28). However, institutions like the Robert Koch Institute (RKI) recommended a PCR confirmation after positive antigen identification (31).

Serologic testing from serum, plasma, or whole blood is not recommended for diagnosis because it takes up to three weeks for seroconversion to occur. Nevertheless, it might be used to gather epidemiologic data about the population percentage, which is vaccinated against, or recovered from a previous SARS-CoV-19 infection. For this purpose, an enzyme linked immunosorbent assay (ELISA) can be used to identify IgM, IgA, and IgG antibodies against the virus. Despite that, there is insufficient evidence for or against serologic testing to gather epidemiologic data regarding previous infection or vaccination (28).

1.1.11 Management

The management of SARS-CoV-19 involves assessing the severity of the individual's condition, which requires a combination of serological and imaging techniques.
For hospitalized patients, additional laboratory investigations are valuable in evaluating organ dysfunction, although they lack specificity for COVID-19. These laboratory tests encompass a complete blood count (CBC), assessment of inflammatory markers, coagulation studies, and analysis of organ function.

Elevated levels of inflammatory markers like interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH), indicate an ongoing COVID-19 infection.
The cytokine IL-6, when binding to the IL-6 receptor of cells, stimulates an immune response by promoting immune cell differentiation, increasing vascular permeability, and triggering the production of inflammatory mediators. Critically ill COVID patients and non-survivors have demonstrated higher levels of IL-6. CRP, released by hepatocytes in response to IL-6, enhances pathogen phagocytosis and activates complement. CRP has also shown a stronger correlation with critical illness compared to age or comorbidities. Ferritin, an acute phase reactant released by macrophages, serves as a predictive factor for COVID mortality risk.

Elevated ferritin levels are often associated with macrophage activation syndrome (MAS), which can occur in critically ill patients. LDH, present in all cells, serves as a prognostic factor for direct tissue damage.

Although most often in the normal range, the white blood cell count (WBC) might be elevated or even decreased in severely ill individuals. The lymphocyte count, however, acts as an important prognostic factor. Critical patients commonly present with lymphopenia and especially low values of $CD4^+/CD8^+$ T-lymphocytes, showing a correlation with mortality. Furthermore, lymphopenia presents as the most common laboratory finding in COVID-19, affecting 60 to 90% of patients.

The hypercoagulable state is reflected by elevated D-dimer, factor VIII, fibrinogen, and von Willebrand factor (vWF) levels with combined thrombocytosis. The elevation of D-dimer has the greatest association with the risk for venous thromboembolism.

SARS-CoV-19 has been shown to have a severe impact on the heart during and after the disease. Therefore, troponin and proBNP (brain natriuretic hormone) serve as useful prognostic markers to assess cardiac function in COVID-positive individuals with cardiac comorbidities.

Acute kidney injury is common among hospitalized patients with SARS-CoV-19. The basic metabolic panel (BMP) is used to evaluate kidney function and may reveal elevated serum creatinine, electrolyte imbalances, and proteinuria/hematuria in urinalysis, indicating renal impairment.

Elevated levels of AST/ALT and decreased albumin levels indicate hepatocyte damage. However, signs of liver damage are uncommon in most COVID patients and are typically observed only in severely ill individuals. Blood cultures or additional sputum analysis may be helpful if a co- or secondary infection is suspected (32). Furthermore, there has been an association shown between low levels of vitamin D in the body and worse disease severity, along with increased mortality (33).

Due to the nonspecific findings, imaging alone cannot confirm or exclude COVID-19 and always requires to be combined with viral testing. Modalities such as chest X-ray, ultrasound, or CT are primarily used for assessing the severity of hospitalized patients (34).

Chest X-rays often fail to detect early lung changes within the first 2-4 days of COVID progression and have lower sensitivity compared to CT scans. Nevertheless, chest X-rays are commonly used as the initial method for assessing pulmonary severity and ruling out differential diagnoses. They can reveal parenchymal changes such as pleural effusion and patchy consolidations, primarily in the peripheral and perihilar regions.

The most effective imaging modality for SARS-CoV-19 assessment is chest CT. CT scans show multifocal lung involvement characterized by a "crazy-paving pattern," consisting of peripheral ground glass opacities and intralobular septal thickening.

Chest ultrasound serves as a rapid alternative to X-ray with higher diagnostic accuracy. It can aid in ruling out differential diagnoses like pneumothorax. Findings that support suspicion of SARS-CoV-2 infection include B lines, pleural thickening, or air bronchograms with small consolidations. Although ultrasound visibility might be limited by air-filled lungs, it is a useful and available diagnostic tool for assessing severity, particularly in the emergency room. However, it is important to note that these findings can also be observed in other viral respiratory infections, so a confirmatory COVID-19 test is still necessary (35).

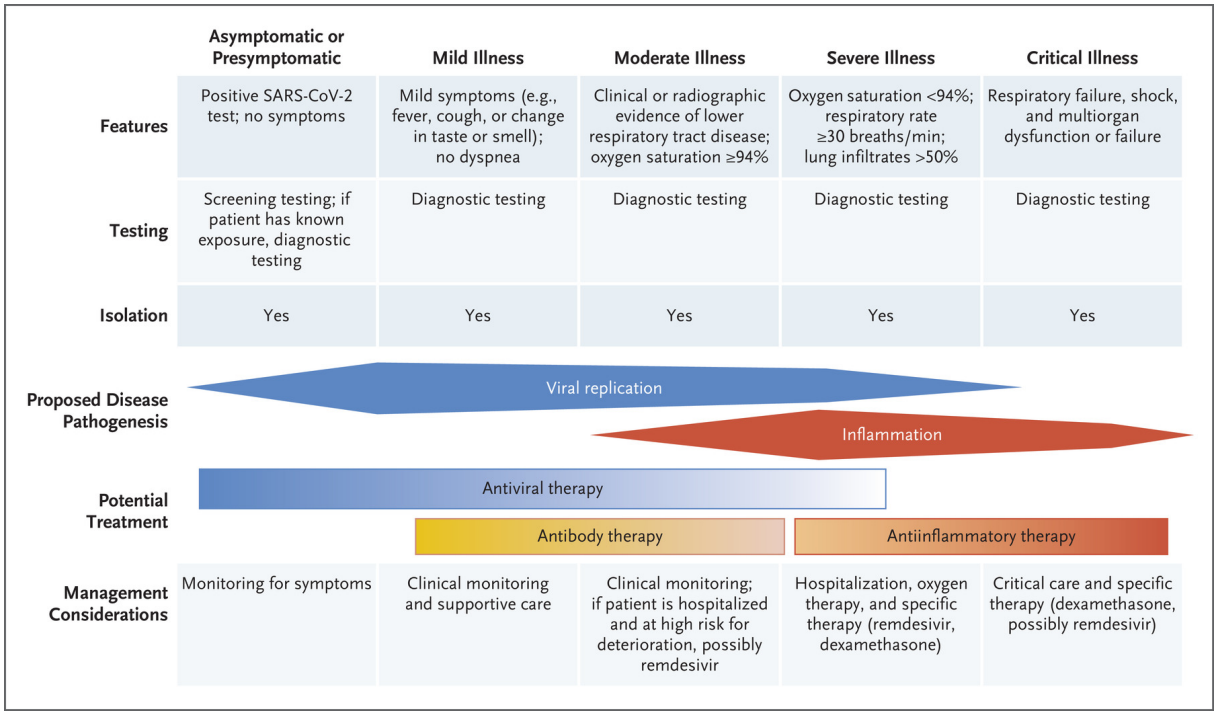

Figure 3. Characteristics, diagnosis, and severity according to COVID severity

Source: Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020 Oct 29;383(18):1757–66.

1.1.12 Treatment

Although the treatment of SARS-CoV-19 varies greatly between different countries and changed multiple times during the course of the pandemic, it is composed of supportive and pharmacological measurements. Supportive care primarily consists of symptomatic therapy in the form of intravenous fluid therapy, antipyretics, analgesics, or antitussives. Adding to that, there is oxygen therapy with the goal to maintain oxygen saturation between 92 to 96%.

Oxygen can either be administered via nasal prongs, high-flow nasal cannula, or non-invasive ventilation. In more severe cases oxygenation is also possible via invasive ventilation in the form of intubation or in the worst cases extracorporeal membrane oxygenation (ECMO) (36).

Pharmacological treatment of COVID involves a combination of antiviral drugs, monoclonal antibodies, corticosteroids, and immunomodulators. The treatment options are based on disease severity and the specific phase of the illness.

The early phase is characterized by increased viral replication, while excessive inflammation and hypercoagulability are signs of the second phase. Antiviral drugs, such as Paxlovid (Nirmatrelvir/Lopinavir), Remdesivir, or Molnupiravir, act as adenosine nucleotide analogs to inhibit viral RNA replicase and replication. These drugs are used in the early phase due to their ability to target viral replication.

Monoclonal antibodies, such as Sotrovimab or Bebtelovimab, target the viral spike protein and their effectiveness is depending on the composition of the spike protein and is thus related to the virus strains. Corticosteroids have been shown to effectively reduce mortality in severe cases of COVID-19 that require oxygen supply or ventilatory support. However, mild cases without supplementary oxygen requirements do not benefit from corticosteroid treatment. Dexamethasone, combined with Remdesivir, is commonly used in moderate to severe cases requiring ventilatory support.

Immunomodulators, like Tocilizumab (an anti-IL-6 monoclonal antibody), act against the IL-6 receptor to decrease inflammation. Janus kinase (JAK) inhibitors, like Baricitinib or Tofacitinib, decrease inflammation and inhibit cytokine signaling and activity (37).

To prevent and treat the hypercoagulable state, anticoagulants, and platelet aggregation inhibitors can be administered. Low molecular weight heparin is the preferred regimen due to its shorter half-life and fewer side effects compared to oral anticoagulants (38). Therapeutic anticoagulation should only be administered in apparent thromboembolic disease.

Treatment decisions should be made by healthcare professionals based on individual patient factors and the evolving understanding of COVID-19 treatment.

1.2 Complications of SARS-COV-2

1.2.1 Direct COVID Complications

Complications of SARS-CoV-2 can manifest in various ways and vary among patients. Due to its involvement in multiple organs, COVID complications can be categorized based on the affected organs.

Neurological long-term effects commonly observed include persistent loss of taste and smell, affecting 11-13.1% of individuals. Other documented symptoms include headache, fatigue, sleep difficulties, cognitive impairments such as memory problems, executive dysfunction, and verbal fluency issues. The prevalence of neuropsychiatric conditions such as PTSD, anxiety, and depression also increased with the virus. These changes can be attributed to a combination of direct viral injury, systemic inflammation, and cerebrovascular alterations.

Dyspnea, or difficulty breathing, is the most common pulmonary complication of COVID, affecting around 22.9-53% of patients even after 2 months from symptom onset.
In some cases, this may lead to long-term reliance on supplemental oxygen (39). Acute respiratory distress syndrome (ARDS) is the most severe complication associated with the disease (37). Pulmonary fibrosis via remodeling of lung tissue, has also been reported.

Cardiovascular complications following COVID infection commonly include chest pain, palpitations, and postural tachycardia syndrome (POTS). Myocarditis, particularly observed in younger athletic individuals following their COVID infection, has been described as a specific cardiac complication (39). Malignant arrhythmias, cardiomyopathy, and cardiogenic shock are additional complications associated with the virus (37).

Due to its ability to induce a hypercoagulable state, the virus is associated with an elevated risk of venous and arterial thromboembolism, including pulmonary embolism and stroke (39). Disseminated intravascular coagulation (DIC) has been identified as a poor prognostic factor and has been observed in 3% of hospitalized patients (37).

The musculoskeletal system, which contains a significant number of ACE2 receptors, is particularly vulnerable to post-COVID complications. Therefore, arthralgia and myalgia are among the most common manifestations during and after the infection. In severe cases, systemic inflammation, malnutrition, and prolonged bed rest lead to catabolic muscle wasting. The presence of the virus in stool samples, even after respiratory testing shows negative results, has been associated with alterations in the microbiome and gastrointestinal symptoms such as diarrhea (39). In severe cases, complications such as bowel ischemia, gastrointestinal bleeding, pancreatitis, intestinal obstruction, or Ogilvie syndrome may occur.

Acute kidney injury is the most frequent extrapulmonary complication of COVID and is associated with a poor prognosis (37). The primary form of kidney damage is acute tubular necrosis. The virus has been linked to new-onset hyperglycemia and the worsening of pre-existing diabetes, including ketoacidosis, due to insulin resistance by the inflammatory state.

COVID-19 increases the risk of secondary invasive fungal infections, particularly when comorbidities such as diabetes are present or with corticosteroid treatment. Examples include rhino-cerebro-orbital mucormycosis and pulmonary aspergillosis. Dermatologic conditions associated with COVID-19 vary among individuals but commonly include temporary hair loss (nonscarring alopecia), maculopapular exanthemas, papulovesicular rash, urticaria, or painful red acral purple papules. Due to increased ACE2 expression in the testes, viral orchitis, as well as reduced levels of testosterone and dihydrotestosterone, have been reported following acute COVID-19 infection (39).

1.2.2 Long-Covid

Although Long-Covid is a part of COVID-19 complications, it deserves a separate discussion. This condition is characterized by long-term health impairments associated with COVID-19, which persist longer than or develop after four weeks following an acute infection.

The clinical presentation of Long-Covid exhibits considerable variability, encompassing differences in psychological and physical symptoms, their frequency, severity, and timing. Consequently, a precise clinical picture cannot be established. If the symptoms persist beyond 12 weeks, it is referred to as Post-COVID Syndrome (40).

Diagnosis relies on a combination of clinical presentation and personal clinical history, as there are no specific clinical examinations to definitively establish the connection between COVID and the occurrence of post-COVID symptoms.

Risk factors for Long-Covid include a severe disease progression, hospitalization or intensive care requirements, preexisting comorbidities, unvaccinated status, or a multisystem inflammatory syndrome (MIS) during or after the disease (41).

The pathogenesis of Long-Covid is not fully understood, but it is believed to involve multiple mechanisms, including immune dysregulation, viral reservoirs in host tissues, alterations in the gut microbiome, dysfunctional neurological signaling, and a hypercoagulative state, all of which contribute to its manifestations. Similar to regular COVID complications, Long-Covid presents with a wide range of symptoms depending on the organs affected (42).

General symptoms of Long-Covid include fatigue or tiredness, fever, and post-exertional malaise, which refers to the worsening of symptoms after physical exercise (41).

As SARS-CoV-2 primarily affects the respiratory system, dyspnea, and cough are the two most common signs of Long-Covid. Neurological symptoms play a significant role and can manifest as cognitive impairment, often referred to as brain fog, along with other possible manifestations such as memory loss, dizziness, ataxia, paresthesia, and changes or loss of smell and taste. Audiovestibular presentations like tinnitus, vertigo, or hearing loss may also occur (42). Other neurological symptoms include headaches, sleeping difficulties, anxiety, and depression.

Long-Covid can also affect the heart, leading to symptoms such as chest pain, palpitations, and postural tachycardia syndrome. Joint or muscle pain, as well as dermatological rash, are additional possible clinical signs (2). Gastrointestinal manifestations may include irritable bowel syndrome, loss of appetite, dyspepsia, or abdominal pain (43).

Due to the presence of ACE2 receptors on ovaries, Long-Covid can also present as menstrual irregularities, with menstruation itself triggering recurring symptoms such as headaches, fatigue, dyspnea, and body pain.

Furthermore, Long-Covid can manifest as a multisystem neuroimmune illness known as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). ME/CFS is characterized by persistent fatigue that is not relieved by rest, sleep disturbances, cognitive impairment, myalgia, and postexertional malaise with exercise intolerance. It is often associated with dysautonomia, mast cell activation syndrome, endometriosis, connective tissue disorders, and neuro-orthopedic spinal/skull conditions (42).

1.3 SARS-CoV-2 Outcome

1.3.1 Prognosis

The factors influencing the prognosis of SARS-CoV-2 can be classified into individual factors, disease complications, changes in CT findings, and laboratory values. The disease outcome strongly depends on individual factors such as age, preexisting comorbidities, and disease severity, including the timing of treatment initiation (44). A higher body mass index (BMI) further worsens the COVID-19 outcome due to impaired immune functioning and reduced lung capacity, making ventilation more challenging (45).

CT findings are most prominent around 10 days after symptom onset and usually resolve within 14 days. Rare CT findings like diffuse alveolar damage and pleural effusion indicate a poor prognosis. Bronchial wall thickening, linear opacities, consolidations, pericardial effusion, lymph node enlargement, and the crazy-paving pattern worsen the prognosis.

The timing, severity, and number of COVID-19 complications, such as disseminated intravascular coagulation (DIC), directly impact the prognosis.

Laboratory values, including abnormal levels of inflammatory markers (CRP, cytokines, ESR), abnormal white blood cell and lymphocyte counts, coagulation studies, and the presence of end-organ damage like acute kidney injury (AKI), are used as predictors of outcome prognosis. Serum antibody levels and titers can also serve as predictive markers (44).

1.3.2 Prevention

During the pandemic, the majority of affected individuals were either asymptomatic (17.9 - 33.3%) or had a mild clinical presentation (37). To limit the spread of the disease, prevent the overload of the healthcare system, and protect those at risk of severe progression or death, several preventive measures were implemented throughout the course of the pandemic.

In addition to general screening and testing for COVID, mandatory isolations were implemented for individuals who tested positive for COVID and their direct contacts. The duration of isolation and the guidelines varied significantly between countries, politics, and the stage of the pandemic but averaged around 14 days in most European countries.

Social distancing and national lockdowns were enforced, with social activities minimized and citizens only allowed to leave their residences for essential purposes such as grocery shopping. Face masks and hand sanitization played a crucial role in limiting the spreading, especially for asymptomatic individuals, and were often mandated in public spaces.

As the SARS-CoV-19 pandemic progressed, vaccination became the most important strategy to control the virus (46). The World Health Organization (WHO) aims to achieve a vaccination rate of at least 70% of the population, with 100% coverage of high-risk groups and healthcare workers receiving their doses (47).

Due to the waning immunity against COVID-19 after two vaccinations, booster doses have been incorporated into the vaccination schedule. Available vaccine types include messenger RNA (mRNA) vaccines, such as Pfizer-BioNTech or Moderna. These vaccines directly instruct the body's muscle cells to produce and express the spike protein found on the surface of COVID-19. As a result, the body generates antibodies against the spike protein, leading to a pre-adapted immune response when the virus enters the body.

Another vaccine option is the vector vaccine, which includes examples like AstraZeneca or Janssen/Johnson & Johnson. The instructions for spike protein expression and antibody development are delivered via a viral vector carrying genetic material from SARS-CoV-2.

The vaccine can also directly deliver the spike protein itself, stimulating antibody production. This type of vaccination is known as a protein subunit vaccine and is administered in the form of the Novavax vaccine (48).

1.4 SARS-CoV-2 Variants

1.4.1 Definition

In March 2023, the WHO updated its classification system, dividing COVID variants into variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). VUMs are characterized as variants with suspected genetic changes in virus characteristics and an alleged growth advantage compared to other variants. However, they lack evidence, and further monitoring is required. On the other hand, VOIs have scientifically proven genetic changes in virus characteristics and growth advantages. If they meet additional criteria such as changes in disease severity, impact on the healthcare system, or reduced vaccine effectiveness, they are classified as VOCs (49).

1.4.2 Alpha Variant

The Alpha variant, also known as the B.1.1.7 lineage, was first identified in the United Kingdom in December 2020. Compared to the original Wuhan strain, this variant contains 15 new mutations, with 8 of them affecting the spike protein, which enhances its binding to the ACE2 receptor and improves cell entry and transmission.

1.4.3 Beta Variant

In October 2020, another variant called Beta or B.1.351 lineage emerged in South Africa. With 9 mutations affecting the spike protein, 3 of them enhanced its binding affinity to the ACE2 receptors. In addition to increased transmission, the Beta variant showed reduced viral neutralization by monoclonal antibodies.

1.4.4 Gamma Variant

The Gamma or B.1.1.28 variant, identified as the third new strain in 2020, was first discovered in Brazil in December. It has 10 mutations affecting the spike protein. Like the Beta variant, three of these mutations enhance ACE2 binding. This new version also exhibits reduced neutralization by monoclonal antibodies and decreased effectiveness of vaccination.

1.4.5 Delta Variant

With 10 mutations in the spike protein, the Delta variant, also known as B.1.617.2, emerged as the fourth and final variant in 2020. It was first discovered in India in December and had a severe impact on the country, quickly spreading worldwide.

1.4.6 Omicron Variant

The current dominant COVID variant is called Omicron, or B1.1.529 lineage. It was first identified in South Africa on November 23 2021., and is characterized by 30 mutations affecting the spike protein. Compared to Delta, Omicron is approximately 2.8 times more contagious. This variant not only exhibits an increased affinity for ACE2 binding and reduced effectiveness in neutralizing monoclonal antibodies but also suggests an increased resistance to vaccines (37).

1.5 Headache

1.6.1 Headache Classification

Headache disorders represent one of the most prevalent pathologies worldwide, characterized by recurring pain in any region of the head. Approximately 50% of the population has reported being affected by headaches at least once per year, while 1.7-4% of the adult population experience headaches at least 15 days per month (50).

Headaches can be classified into two categories: primary and secondary headaches. Primary headaches include migraine, tension-type headache (TTH), and cluster headache. Secondary headaches encompass various etiologies, including vascular, traumatic, infectious, ischemic, immune-related, or pressure-related causes. Among primary headaches, with the exception of cluster headache, all types are more prevalent in women, with tension-type headache having the highest overall prevalence. Clinical diagnosis serves as the initial step in identifying primary headaches.

1.6.2 Tension-Type Headache (TTH)

Tension-Type Headache (TTH) is characterized by a persistent, dull, non-pulsating pain that occurs in a band-like pattern, either holocranial (around the entire head) or bifrontal (across the front of the head). The duration of TTH episodes can range from 30 minutes up to 7 days. Although the pain severity is usually mild to moderate, the attacks occur daily and persist until their end. TTH can manifest as either episodic or chronic.

Additional common symptoms include tightness in the muscles of the posterior neck or tenderness in the pericranial area, as well as sensitivity to sound (phonophobia) or light (photophobia). It's important to note that phonophobia and photophobia do not typically occur simultaneously; their simultaneous presence suggests a migraine rather than TTH. Risk factors or triggers for TTH include stress, anxiety, depression, fatigue due to lack of sleep, and poor posture (51).

TTH can be classified into two types. The episodic type can be infrequent, with episodes occurring less than 1 day per month or less than 12 days per year. Alternatively, it can be frequent, with episodes lasting 1 to 14 days per month and occurring more than 12 but less than 180 days per year. The chronic type of TTH is characterized by a frequency of more than 15 days per month, lasting longer than 180 days per year (52). Management of TTH involves identifying and avoiding triggers, making lifestyle modifications, and for episodic TTH, over-the-counter pain relievers such as NSAIDs or acetaminophen can be effective. However, chronic TTH often requires preventive therapy, such as the use of medications like amitriptyline.

1.6.3 Migraine

Migraine is characterized by episodic occurrences, with or without preceding aura, that can occur occasionally or multiple times per month and typically last from 4 to 72 hours. If a headache lasts longer than 72 hours, it is highly unlikely to be a migraine. Unlike TTH, migraine pain usually occurs on one side of the head and is of moderate to severe intensity. In addition to aura, prodrome symptoms such as mood changes, changes in appetite (excessive or lack of), as well as difficulties with writing or reading, may also occur. During a migraine episode, pain can be accompanied by hyperacusis, photophobia, or phonophobia. After symptoms subside, a postdrome phase follows, which involves weakness, exhaustion, or even euphoria.

Effective prevention of migraine attacks involves identifying and limiting triggers. These triggers may include stress, hormonal fluctuations (such as those caused by oral contraceptives), exercise, or consumption of foods containing tyramines or nitrates. When an attack is classified as mild to moderate and does not significantly interfere with daily activities, it can be managed with over-the-counter pain relievers such as NSAIDs, acetaminophen, or even caffeine. In cases where migraine attacks significantly impair daily life, medications like metoclopramide (an antidopaminergic) or migraine-specific agents such as triptans or ergotamine can be administered.

1.6.4 Cluster-Type Headache

Although cluster-type headache is believed to have a genetic component, it is triggered by various factors such as alcohol, histamines, nitroglycerine, or volatile substances.
Seasonal fluctuations have also been linked to cluster headaches, with attacks being more common in spring and autumn.

Characteristic features of cluster headaches include short, recurrent attacks that follow a cycling pattern, occurring up to 8 times per day and lasting from 15 to 180 minutes. Cluster headaches can be classified based on remission periods lasting longer (episodic) or shorter (chronic) than 3 months. The pain is described as burning or piercing and is extremely severe, exclusively occurring on one side of the head in the periorbital and temporal region. Additional symptoms may include a combined Horner syndrome, ipsilateral conjunctival injection, lacrimation, rhinorrhea, and nasal congestion (51).

Similar to migraines, cluster headaches can be treated with triptans. However, the first-line management for cluster headaches involves the inhalation of 100% oxygen. Preventive treatments for cluster headaches include verapamil, lithium, and topiramate (53).

1.6.5 COVID Headache

During the acute phase of the disease, 14-60% of individuals present with a headache characterized by a pressing pain located in the upper frontal head. Headache is the 5th most common long-COVID symptom, following fatigue, dyspnea, myalgia, and cough. It shares similarities with new daily persistent headache.

There is no significant difference in prevalence between non-severe and severe disease progression; however, the elderly and women are more often affected. Possible hypotheses for its pathophysiology include the activation of the trigeminovascular system in individuals with a preexisting genetic risk for migraine, an excessive immune response, and structural changes in the brain's gray matter. Headache during the disease has been identified as a positive prognostic factor, associated with lower levels of D-dimer, CRP, lactate dehydrogenase, and ferritin, as well as elevated levels of lymphocytes. Although the clinical presentation of long-COVID headache varies, it is often accompanied by fatigue, cognitive dysfunction, dizziness, sleep impairments, or hyposmia/anosmia. The pain is described as pressing and located in the frontal and periocular areas. One-third of individuals experience throbbing pain in the occipital area. The headache can resemble primary headaches such as migraine or, more commonly, TTH, with co-symptoms like photo-/phonophobia, nausea, vomiting, or exercise exacerbation.

Diagnosis is based on the exclusion of other primary and secondary headache causes. Treatment involves the use of NSAIDs for pain management, as well as specific preparations for migraines or TTH. In cases of TTH phenotype, glucocorticoids can improve symptom severity, and tricyclic antidepressants like amitriptyline can be used as prophylactic therapy for tension-type headaches and migraines. Triptans and indomethacin have also been suggested for migraine presentations and onabotulinumtoxin A acts as prophylactic management (54).

2. OBJECTIVES

2.1 Aims of the Study

The aim of the study is to collect new and additional data on post COVID period, specifically focusing on symptom prevalence, gender differences, and duration, while comparing different virus variants. The study aims to investigate the symptom of headache and its potential correlation with influencing parameters and concurrent symptoms including its correlation to fatigue and tiredness.

The primary objectives of the provided information are to conduct a comprehensive analysis of the study population and explore various aspects related to demographics, vaccination status, and the prevalence and duration of headaches. The study aims to provide insights into these areas by examining the data collected from the survey participants.

The demographic analysis focuses on the composition of the study population, including the number of excluded patients and the reasons for their exclusion. It also presents information about the gender and age distribution of the respondents, as well as the response rates observed during different phases of the study.

Regarding vaccination status, the research delves into the number of individuals who received different doses of the vaccine, shedding light on the vaccination rates among the survey participants.

The study further explores the prevalence and duration of headaches among the survey participants. It examines the occurrence of headaches and analyzes any potential gender-related differences. Additionally, the duration of headaches is considered, and statistical tests are employed to evaluate the association between headache occurrence and duration with gender. Furthermore, the analysis extends to the different phases of the study. The prevalence and duration of headaches are examined across these phases, and statistical tests are employed to explore any potential associations with influencing factors.

Overall, the study aims to provide a comprehensive understanding of the demographic characteristics of the study population, their vaccination status, and the prevalence and duration of headaches. It also seeks to explore potential associations between these variables, particularly in relation to gender and the different phases of the study.

2.2 Hypothesis

Prevalence and duration of post-COVID-19 symptoms vary between the different variants of SARS-CoV-2.

3. MATERIAL AND METHODS

3.1 Study Design

The study was designed as a retrospective cross-sectional survey study and conducted in the rural region in and around Coburg, Bavaria, Germany, with patients admitted to the REGIOMED Hospital Coburg. Its data was obtained from the study getting anonymized, ensuring that no conclusions could be drawn about personal patient information. The collected data sets were categorized into 4 groups based on the classification of phases during the COVID-19 pandemic, as provided by the Robert Koch Institute (Table 1.) (55). Phase 1 of the study encompassed the SARS-CoV-2 wild type and spanned from the occurrence of the first sporadic cases in the 5th calendar week (CW) of 2020 until CW 8, 2021. The second phase focused on the alpha variant, lasting from CW 9, 2021 until the 30th week of 2021. Phase 3 began with the delta variant in CW 31, 2021, and continued until CW 51 of the same year. The fourth and final phase of the study examined the Omicron variant, covering the time period from CW 52, 2021 until the end of sample collection in March 2022.

Table 1. Classification of phases regarding COVID-19 distribution in Germany

Phase	***Name***	***Variant of Concern***	***Start (CW)***	***End (CW)***
0	Sporadic Cases	Wild Type	05/2020	09/2020
1	First COVID-19 Wave	Wild Type	10/2020	20/2020
2	Second COVID-19 Wave	Wild Type	40/2020	08/2021
3	Third COVID-19 Wave	Alpha	09/2021	30/2021
4	Fourth COVID-19 Wave	Delta	31/2021	51/2021
5	Fifth COVID-19 Wave	Omicron	52/2021	21/2022

3.2 Data Collection

The study data was obtained by combining the hospital's data with information acquired via an online survey. The target population includes 1430 former patients hospitalized with the ICD code for SARS-CoV-2 (U07.1) as either the main or secondary diagnosis during the time period from the 16th of March 2020 until the 30th of March 2022. In order to maintain a pseudo-anonymized data collection, each participant got assigned to an individual case number, allowing only the physician to evaluate.

From the target group, 1025 participants received a cover letter with an invitation, introduction, instruction and QR-code/link to be forwarded to an online survey conducted with the survey system LamaPoll, from which the data was collected. In order to improve the participation rate of older individuals who lack digital access to the questionnaire, a prepaid return envelope containing a printed version of the same questionnaire was included in the letter. This enables participants to conveniently complete the survey and send it back by mail, eliminating the need for digital resources. The remaining 405 individuals from the target population got excluded due to low/no chances of a response. In the end, the responses from pediatric patients got excluded and a total of 147 survey responses got collected, with a response rate of 14.3%.

To allow anonymous association with each individual, every participant was required to enter his or her personal case number as security at the beginning of the survey.
Furthermore, information was acquired from all 1430 participants via the clinic´s information system, Orbis, powered by Dedalus, in which the patients were identified via the built-in search and filter function with their case number.

For the final analysis pediatric patients, individuals without proof of a positive PCR test and participants who got tested positive for COVID on the day of discharge got excluded from the analysis. Subtracting the excluded patients, for final analysis, combined Orbis and survey data were only used from the 147 survey responses.

3.3 Variables

The survey presents a comprehensive analysis of the presentation and characteristics of patients previously hospitalized with SARS-CoV-2. Each participant was advised to answer the questions based on their personal experience after the COVID infection.

The survey included general questions about risk factors such as gender, education, nutrition, smoking history in pack years, and alcohol consumption per day and week.

Additionally, participants were asked about their pre- and post-infection lifestyle, including exercise activity level per week (very active, active, less active, not active), changes in general health status (improved, remained the same, or reduced), concentration abilities, psychological status, changes in body weight (in kilograms), and presence of pain on a numeric pain scale. Information about vaccination status was collected and categorized as one dose, two doses, booster dose, immunity due to recovery from COVID-19, or unvaccinated. The vaccination status did not include the classification regarding the type of vaccine.

The survey also inquired about pre-existing health conditions and medications used. Data on Long-Covid were obtained by asking about common general symptoms (fatigue, hair loss, chest pain, tiredness, fever, myalgia/arthralgia, nausea/vomiting), pulmonary presentations (rhinitis, cough, sore throat, dyspnea), neurological manifestations (headache, forgetfulness, anosmia, loss of taste, vertigo), psychological effects (anxiety/panic, sadness, sleeping problems), and cardiovascular problems such as hypertension, hypotension, tachycardia, arrhythmic pulse, or no problems.

The duration of Long-Covid symptoms was also assessed and categorized as lasting 1-4 weeks, 4-12 weeks, or longer than 12 weeks. This classification is based on the RKI definitions for acute post-COVID referring to symptoms lasting up to 4 weeks, as well as Long-COVID which is characterized by symptoms that persist or develop within 4 to 12 weeks after the infection, and the Post-COVID syndrome which refers to symptoms which are present after 12 weeks without any other explanation.

Apart from the survey, the Orbis system was used to collect and analyze the participants' data. This included information such as the date of PCR testing, the presence of symptoms during admission, vaccination status, weight, height, and BMI. Additionally, data was collected on whether the individuals were admitted to the intensive care unit (ICU). For those who had an ICU stay, information on the duration and any ventilatory support received was recorded.

3.4 Ethical Approval

The research plan that had been prepared in advance was submitted to the Institutional Review Board (IRB) of the Medical School Regiomed Coburg. In accordance with §2 of the IRB's regulations, no objections were raised regarding the implementation of the research project. The study was conducted in adherence to the principles outlined in the Declaration of Helsinki.

3.5 Statistical Analysis

The statistical analyses of the variables and phases were conducted using Stata 16 Statistics (Stata Corporation, College Station, TX, USA).

In order to assess and compare the samples regarding their variables, descriptive statistics in the form of mean, median, standard deviation, minimum and maximum were used.

For comparison and assessment of the significance regarding the distribution of the independent variables, as no normal distribution could be assumed, data were analyzed using the Mann-Whitney U test. To test for the presence of an association or relationship between two categorical variables, the chi-squared test was used. The significance level was set at a p-value of <0.05. Furthermore, to analyze the association between two categorical variables, in four-field tables, the study used the Fisher's exact test

4. RESULTS

4.1 Demographic Analysis

4.1.1 Excluded Patient Sample

The study included 1430 former SARS-CoV-2 hospitalized patients, out of which 405 individuals were excluded from the analysis due to low/no chances of response before the cover letter was addressed. As shown by Figure 4 and Table 2, within the excluded sample of 405 individuals (100%), there were 56 cases (13.8%) of patients who didn´t meet the inclusion criteria, 76 cases (18.8%) from a nursing facility, 3 cases (0.7%) with an outcome of respiratory rehabilitation, and 270 cases (66.7%) of deceased patients.

Figure 4. Consort diagram of the study population

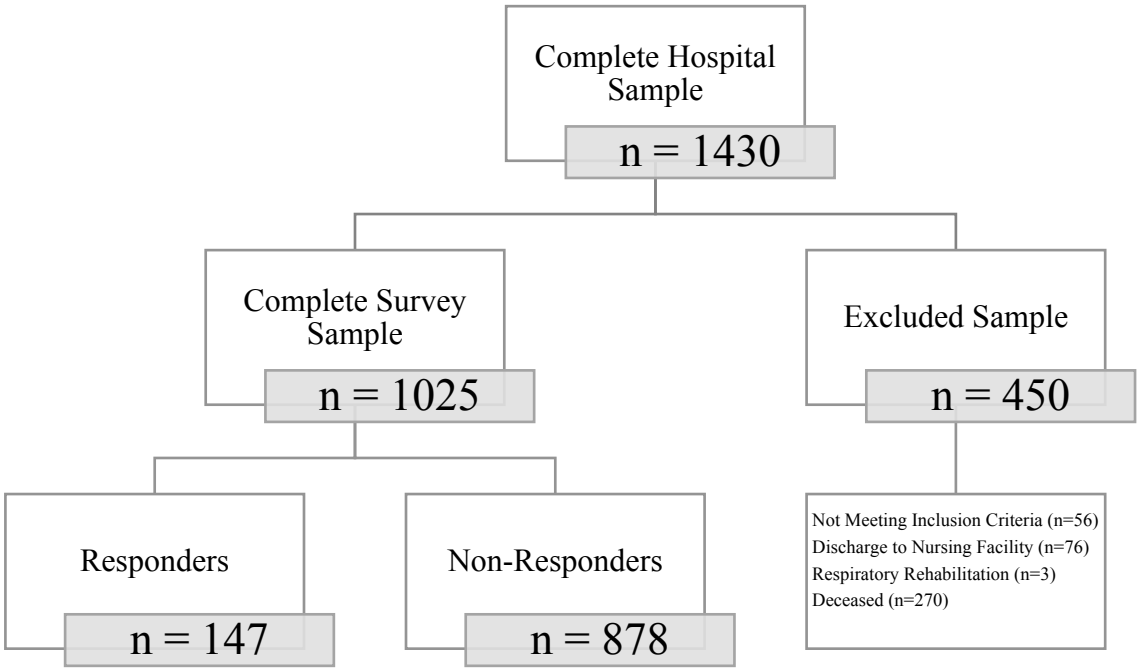

Table 2. Division of the excluded sample

Excluded Sample	*405*	*100%*
Discharged Against Medical Advice	56	13.8%
Care Facility	76	18.8%
Ventilatory Rehabilitation	3	0.7%
Deceased	270	66.7%

4.1.2 Collected Survey Answers

The remaining 1025 individuals (100%) received their cover letters, and the answers were collected from September 2022 to December 2022. Among the sample group, 147 responses (14.3%) were gathered, while the remaining 878 cases (85.7%) did not provide a response. Table 3 summarizes and compares the response rates across the different phases, showing the greatest response in numbers from Phase 1 (63), while the greatest response in percentage stems from Phase 2 (19.9%).

Table 3. Answer distribution from the total sample and across the phases

	Total Sample	*Phase 1*	*Phase 2*	*Phase 3*	*Phase 4*
Total Sample	1025 100%	406 100%	156 100%	204 100%	259 100%
Missing Answers	878 85.7%	343 84.5%	125 80.1%	179 87.8%	231 89.2%
Answers	147 14.3%	63 15.5%	31 19.9%	25 12.3%	28 10.8%

4.1.3 Gender Distribution Across Answered Surveys and Phases

The 147 completed surveys (100%) were divided into 80 males (54.4%) and 67 females (45.6%) who responded, indicating a relatively equal distribution of gender within the sample. Taking a closer look at the gender distribution among the participants in the different phases, Table 4 displayed the highest proportion of males in Phase 3 (68.0%), while Phase 4 had the highest percentage of females (50.0%). Combining these results, we observe that there are no apparent differences in the distribution of individuals across phases based on gender. This is supported by the similar column percentages, indicating consistent gender representation across the different phases. The non-significant chi-square test result with a p-value of 0.516 further reinforces the lack of a significant relationship between gender and phase.

Table 4. Gender distribution across the answered surveys and the phases

	Answered Surveys	*Phase 1*	*Phase 2*	*Phase 3*	*Phase 4*
Answered Surveys	147 100%	63 100%	31 100%	25 100%	28 100%
Male	80 54.4%	33 51.4%	16 51.6%	17 68.0%	14 50.0%
Female	67 45.6%	30 47.6%	15 48.4%	8 32.0%	14 50.0%

4.1.4 Age Distribution Across the Answered Surveys and Phases

When analyzing the response rate with respect to age distribution, the participants who responded to the survey had a mean age of 65.13 years (SD = 15.4) (Table 5). On the other hand, the group of 878 cases with no response presented a mean age of 67.39 years (SD = 19.17). In order to compare the response rate and age distribution, a Mann-Whitney U test was conducted. The test yielded a z-value of 2.620, indicating a significant difference in rank sums between the responding and non-responding groups. The p-value of 0.0088 further supports this finding, indicating a statistically significant different age between the two groups.

It can be concluded, that the respondents tended to be slightly younger, with a lower mean age compared to the non-respondents. This information suggests that age may play a role in survey participation and should be considered when interpreting the survey results.

The study also analyzed the age distribution of survey participants across the four phases. For Phase 1, the mean age of the responders in this phase was 66.46 years, with a standard deviation of 13.52 years, while the survey participants in Phase 2 presented with the youngest mean age of 60.87 years (SD = 15.37). In Phase 3, the mean age for the responders was 65.2 years (SD of 17.25) and among the participants who responded to the survey in Phase 4, the mean age was the oldest, with 66.79 years and a standard deviation of 17.56 (Table 5).

Table 5. Age distribution across the answered surveys and the phases in years

	Answered Surveys	*Unanswered Surveys*	*Phase 1*	*Phase 2*	*Phase 3*	*Phase 4*
Mean Age	65.12925	67.3918	66.46	60.87	65.2	66.79
Standard Deviation	15.40204	19.17195	13.52	15.37	17.25	17.56
Minimum Age	21	18	34	23	27	21
Maximum Age	94	101	94	83	87	86
Median Age	65	72	65	62	68	71

Table 6. Immunization status from the survey participants divided by gender

	Male Gender	*Female Gender*	*Total Sample*
Not Immunized	45 57.7%	49 74.2%	94 65.3%
One Immunization	10 12.8%	1 1.5%	11 7.6%
Two Immunizations	13 16.7%	8 12.1%	21 14.6%
Three Immunizations	10 12.8%	8 12.1%	18 12.5%
Total Sample	78 100%	66 100%	144 100%

4.1.5 Immunization Status from the Survey Participants

Apart from gaining demographic data regarding gender and age, participants were also surveyed for their immunization status. It is important to mention, that vaccination, as well as natural gained immunity from COVID-19 recovery, was counted as one immunization event.

Thereby, the 144 participants (100%), who answered this question got divided into individuals having received 1, 2, 3 doses, or no immunization event. The sample furthermore got distributed into males and females regarding their immune status (Table 6.).

Combining these results, the study and data collected stem to 66% of participants without an immune status due to more answers being collected from this group. Furthermore, a greater number of females presented as not immunized compared to the males.

4.2 Headache Prevalence and Duration in General

4.2.1 Headache Prevalence Regarding Gender Distribution

Out of the 147 survey participants (100%), respondents were divided by gender in terms of headache prevalence (Table 7).

Analyzing the column percentages for the presence or absence of headache, out of the 112 participants without a headache (100%), 65 participants (58.0%) were males, and 47 participants (42.0%) were females. Among the 35 participants with a headache (100%), 15 participants (42.9%) were males, and 20 participants (57.1%) were females.

The Pearson chi-square test was performed to investigate the relationship between headache and gender. The test resulted in a chi-square statistic of 2.4769 with 1 degree of freedom and a p-value of 0.1155. Based on these findings, there is no strong evidence to support a significant association between headache and gender. In summary, the analysis suggests that there is no significant link between gender and the occurrence of headache among the participants surveyed.

Table 7. Headache prevalence divided by gender

	Male Gender	*Female Gender*	*Total Sample*
Headache No	65 81.3%	47 70.1%	112 79.2%
Headache Yes	15 18.8%	20 29.9%	35 23.8%
Total	80 100%	67 100%	147 100%

Table 8. Headache duration divided by gender

	Male Gender	Female Gender	Total Sample
Headache No	65	47	112
	81.3%	70.1%	79.2%
Duration Less	4	9	13
Than 4 Weeks	5.0%	13.4%	8.8%
Duration 4	4	3	7
to 12 Weeks	5.0%	4.5%	4,8%
Duration More	7	8	15
Than 12 Weeks	8.8%	11.9%	10.2%
Total	80	67	147
Sample	100%	100%	100%

4.2.2 Headache Duration Regarding its Differences Among Genders

In addition to the prevalence, the duration of headache and distribution differences among males and females got examined. Therefore, the sample was divided into 4 groups based on the duration of headaches: participants with no headache, headache for less than 4 weeks, headache from 4 to 12 weeks, and headache persisting for longer than 12 weeks (Table 8).

In order to assess the association between headache and gender a Pearson chi-square test was conducted. The test yielded a chi-square statistic of 3.9063 with 3 degrees of freedom and a p-value of 0.272. The p-value suggests no significant association between the duration of headaches and gender, as it was greater than the conventional significance level of 0.05.

In summary, the analysis indicates no significant relationship between the duration of headaches and gender among the surveyed participants.

4.3 Headache Prevalence and Duration per Phase

4.3.1 Headache Prevalence with Distribution per Phase

Comparing the distribution of headaches among the different phases (Table 9), the following observations were made. While Phase 1 had the highest proportion of headaches (31.8%), the prevalence decreased in a non-linear fashion in the remaining phases, with the lowest prevalence observed in Phase 3 (12.0%).

To assess the association between the different phases and the occurrence of headaches, a chi-squared test was conducted. The test yielded a statistic of 5.578 with 3 degrees of freedom and a p-value of 0.134. In summary, based on the analysis and the p-value of 0.134, there is no significant association between the occurrence of headaches and the phases examined.

Table 9. Headache prevalence divided by phase

	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Total Sample*
Headache No	43 68.3%	23 74.2%	22 88.0%	24 85.7%	112 79.2%
Headache Yes	20 31.8%	8 25.8%	3 12.0%	4 14.3%	35 23.8%
Total Sample	63 100%	31 100%	25 100%	28 100%	147 100%

4.3.2 Headache Duration with Distribution per Phase

Besides examining the prevalence of headaches across different phases, the study also investigated the variation in headache duration among the four phases, using the same time intervals as in section 4.2.2 (Table 10). Comparing the four phases, the duration of headaches decreased from Phase 1 to Phase 4, with no cases of headaches lasting longer than 4 weeks in Phases 3 and 4.

Similar to the distribution of headaches as a symptom, the results of the Pearson chi-square test indicated no significant association between headache duration and the phases of the study. The test yielded a chi-square statistic of 10.3484 with 9 degrees of freedom and a p-value of 0.323. Therefore, there is insufficient evidence to suggest a significant relationship between headache duration and the phases of the study.

Table 10. Headache duration divided by phase

	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Total Sample*
Headache No	43 68.3%	23 74.2%	22 88.0%	24 85.7%	112 79.2%
Duration Less Than 4 Weeks	6 9.5%	2 6.5%	2 8.0%	3 10.7%	13 8.8%
Duration 4 to 12 Weeks	5 7.9%	1 3.2%	0 0.0%	0 0.0%	7 4.8%
Duration More Than 12 Weeks	9 14.3%	5 16.1%	0 0.0%	0 0.0%	15 10.2%
Total Sample	63 100%	31 100%	25 100%	28 100%	147 100%

4.4 Headache in Relation to Tiredness and Fatigue

Fatigue and tiredness were two commonly described Long-Covid symptoms in the survey. Out of the 147 participants, 101 experienced fatigues to some degree, while 97 out of 145 individuals reported tiredness. To further investigate the prevalence and duration of Long-Covid, the study also examined the possible association between these symptoms and headache.

4.4.1 Headache in Relation to Tiredness

Among the 145 individuals who responded to the question, 32 cases reported having both tiredness and headache (Table 11). The chi-square test results indicated a significant association between the overall headache and tiredness at a 0.05 significance level ($p < 0.05$). The test statistic was calculated as 10.4595, with a corresponding p-value of 0.001.

The data was further analyzed in different phases (Table 8.). The chi-square tests revealed a significant association between headache and tiredness in Phase 1, as well as in Phase 4. In comparison, Phase 2 and Phase 3 presented without a relation. Nevertheless, the combined observed frequencies in the dataset (p-value = 0.05, Pearson chi2 = 10.4595) show, that individuals who reported having a headache were more likely to also report feeling tired, while those without a headache were less likely to report feeling tired. In other words, the presence of a headache is associated with an increased likelihood of experiencing tiredness.

Table 11. Headache association with tiredness

	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Total Sample*
Total Headache (- = No, + = Yes)	- 42 + 20	- 23 + 8	- 21 + 4	- 23 + 4	- 109 + 36
Total Tiredness (- = No, + = Yes)	- 14 + 48	- 9 + 22	- 9 + 16	- 16 + 11	- 48 + 97
Only Headache	1	1	2	0	4
Only Tiredness	29	15	14	7	65
Headache and Tiredness	19	7	2	4	32
No Headache and No Tiredness	13	8	7	16	44
Pearson Chi2	5.2198	1.4304	0.4051	6.8300	10.
p-Value	0.022	0.232	0.524	0.009	0.001
Total Sample	62	31	25	27	145

4.4.2 Headache in Relation to Fatigue

Out of 147 individuals in the study, 33 individuals reported both fatigue and headache (Table 12). The chi-square test revealed a significant association between headache and fatigue in the overall sample, with a p-value of 0.001 and a test statistic of 11.688, indicating a meaningful relationship between headache and fatigue. Further examination of the different phases showed that the association between headache and fatigue was statistically significant only in Phase 1 (p-value = 0.025). No statistically significant associations were found in Phases 2, 3, and 4. The findings suggest a significant association between headache and fatigue. In the overall sample, individuals who reported having a headache were more likely to also report feeling fatigued.

This indicates that experiencing a headache is linked to an increased likelihood of experiencing fatigue. However, the significance of the association varied across different phases. Phase 1 showed a significant association between headache and fatigue, while the other phases did not demonstrate a significant relationship. This suggests that the relationship between headache and fatigue may be influenced by different factors or circumstances in each phase. In summary, the presence of a headache is generally associated with an increased likelihood of experiencing fatigue. However, the specific nature and strength of this association may vary depending on the phase or other factors considered in the analysis.

Table 12. Headache association with fatigue

	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Total Sample*
Total Headache (- = No, + = Yes)	- 43 + 20	- 23 + 8	- 21 + 4	- 24 + 4	- 111 + 36
Total Fatigue (- = No, + = Yes)	- 14 + 49	- 7 + 24	- 8 + 17	- 17 + 11	- 46 + 101
Only Headache	1	0	1	1	3
Only Fatigue	30	16	14	8	68
Headache and Fatigue	19	8	3	3	33
No Headache and No Fatigue	13	7	7	16	43
Pearson Chi2	5.0285	3.1449	0.1072	2.4955	11.6887
p-Value	0.025	0.076	0.743	0.114	0.001
Total Sample	63	31	25	28	147

4.5 Headache Association With Age

After determination of the participant's age distribution, the study questioned, whether or not age has a potential influence on headache prevalence and occurrence (Table 13). Individuals without headache had a mean age of 66.41, with a standard deviation of 15.50 years. In contrast, survey participants with headache as Long-Covid symptom were characterized by a mean age of 61.03 years (SD = 14.53). Participants with headaches tended to be younger on average, have a slightly lower maximum age, and a lower median age compared to participants without headaches.

However, both groups exhibited similar levels of variability in terms of age distribution, as indicated by their comparable standard deviations. A two-sample Wilcoxon rank-sum test (Mann-Whitney U test) was performed, comparing the occurrence of headache with age to determine if there was a significant difference in the distribution of age between the two groups. Based on the test results, the test statistic (z) was calculated to be 2.059 with the probability (p-value) of obtaining a test statistic as extreme as z or more extreme was found to be 0.0395. Thus, we reject the null hypothesis and conclude that there is evidence of a statistically significant difference in age between the two groups with and without headache.

Table 13. Age distribution between survey participants with and without headache

	Headache Present	*Headache Absent*	*Overall Sample*
Mean Age	61.03	66.41	65.13
Standard Deviation	14.53	15.50	15.40
Minimum Age	23	21	21
Maximum Age	85	94	94
Median Age	85	94	65

4.6 Headache as Comorbidity and Long-Covid Symptom

In order to identify a possible connection between headache already being present before the SARS-CoV-2 infection and headache as Long-Covid symptom, the study analyzed a total sample of 145 participants who answered both questions (Table 14). Out of the 17 participants who reported having a preexisting headache, 12 experienced headaches after their COVID infection. To assess the association between these variables, Fisher's exact test was performed. In this analysis, the Fisher's exact test resulted in a p-value of less than 0.001.

Based on the provided table and the result of Fisher's exact test, strong evidence suggests a significant association between having a preexisting headache and experiencing headaches in the given sample. This indicates that there is a greater probability of experiencing headaches as a symptom of Long-Covid if an individual already has a preexisting headache.

Table 14. Headache association with headache as a preexisting condition (comorbidity)

	Headache Absent	*Headache Present*	*Total Sample*
Comorbidity Absent	105 95.5%	23 65.7%	128 88.3%
Comorbidity Present	5 4.6%	12 34.3%	17 11.7%
Total Sample	110 100%	35 100%	145 100%

Table 15. Headache association with anosmia

	Headache Absent	*Headache Present*	*Total Sample*
Anosmia Absent	78 69.6%	14 40.0%	92 62.6%
Anosmia Present	34 30.4%	21 60.0%	55 37.4%
Total Sample	112 100%	35 100%	147 100%

4.7 Headache and Anosmia

With anosmia being another common Long-Covid symptom, 55 out of the 147 survey participants experienced a loss of smell after their infection. Among the 35 participants who reported having a headache, 14 participants did not experience anosmia, accounting for 40% of the total sample. Furthermore, among the participants with a headache, 21 participants reported anosmia, representing 60% of the total sample (Table 15). The Fisher's exact test determined the association between headache and anosmia. The Fisher's exact test resulted in a p-value of 0.002, indicating a significant association between the variables and indicating a noteworthy relationship between experiencing a headache and reporting anosmia symptoms.

4.8 Headache and Smoking

Of the 50 participants, who reported as smokers, 11 (31.4%) also presented with post-COVID headache (Table 16). Former smokers were included in the sample of 97 non-smokers. To identify a possible connection between headache and smoking, the Pearson's chi-square test was conducted. The test resulted in a chi-square value of 0.1368 with a corresponding p-value of 0.712. Therefore there was no significant association between experiencing a headache and being a smoker in the given sample.

Table 16. Headache association with smoking

	Headache Absent	*Headache Present*	*Total Sample*
Non-Smokers	73	24	97
	65.2%	68.6%	66.00%
Smokers	39	11	50
	34.8%	31.4%	34.0%
Total Sample	112	35	147
	100%	100%	100%

4.9 Headache and Alcohol Consumption

Besides a relationship between headache and smoking, the study analyzed the connection between headache and alcohol consumption (Table 17). Of the participants presenting with headache, 18 individuals (51.4%) did consume alcohol.

With the Pearson's chi-square test, the association between headache and alcohol consumption resulted in a test value of 0.7919 and a corresponding p-value of 0.374.
Based on this p-value, there is no significant evidence to support an association between experiencing a headache and alcohol consumption in the given sample.

Table 17. Headache association with alcohol consumption

	Headache Absent	*Headache Present*	*Total Sample*
No Alcohol Consumption	48 42.9%	17 48.6%	66 44.9%
Alcohol Consumption	64 57.1%	18 51.4%	81 55.1%
Total Sample	112 100%	35 100%	147 100%

Table 18. Headache association with immunization status

	Headache Absent	*Headache Present*	*Total Sample*
Not Immunized	58 75.3%	19 24.7%	77 100%
Single Immunization	3 75.0%	1 25.0%	4 100%
Two Immunizations	11 78.6%	3 21.4%	14 100%
Three Immunizations	13 81.3%	3 18.8%	16 100%
Total Immunizations	85 76.6%	26 23.4%	111 100%

4.10 Headache and Immunization

More than half of the survey participants lacked some form of COVID immunity, either through vaccination or post-infectious acquired immunity. Therefore, the study analyzed the association between headache and immunization. Due to some participants not answering this question, the total sample included 111 cases. Among them, 85 participants did not have a headache, while the remaining 26 participants reported experiencing headache (Table 18).

The Pearson's chi-square test examined the possible association between headache and immunization status. The chi-square test resulted in a chi-square value of 0.2987 with a corresponding p-value of 0.960. Based on this p-value, there is no significant evidence to suggest an association between experiencing a headache and the immunization status in the given sample.

4.11 Logistic Regression Analysis of Headache

The logistic regression analysis aimed to predict the likelihood of experiencing Long-Covid headache based on the simultaneous existence of preexisting headache, tiredness, and anosmia. The results indicate that preexisting headache, tiredness, and anosmia are statistically significant predictors of Long-Covid headache (Table 19).

Individuals with a preexisting headache are approximately 15.05 times more likely to experience Long-Covid headache compared to individuals without a preexisting headache. Tiredness increases the likelihood of Long-Covid headache by 6.73 times, and the presence of anosmia is associated with a 2.99 times higher likelihood of experiencing Long-Covid headache. The statistical significance of these associations suggests, that preexisting headache, tiredness, and anosmia are relevant factors in predicting an increased likelihood of Long-Covid headache.

However, it's essential to consider the limitations of the analysis, such as potential confounding factors and the specific context in which the analysis was conducted. Additionally, further investigation and analysis are necessary to gain a comprehensive understanding of the relationships between the 3 variables and the specific outcome of Long-Covid headache.

Table 19. Logistic regression analysis of headache

	Odds Ratio	*Standard Error*	*z-Score*	*p-Value*	*95% Confidence Interval*
Preexisting Headache	15.052	10.217	3.99	0.000	3.980
Tiredness	6.730	4.852	2.64	0.008	1.638
Anosmia	2.991	1.404	2.33	0.020	1.192
Cons	0.0281	0.020	-4.90	0.000	0.007

5. DISCUSSION

5.1 Discussion of the Study

The present study aimed to investigate the prevalence and characteristics of headaches as a symptom of Long-Covid among former SARS-CoV-2 hospitalized patients. Thereby the survey targeted to collect new and additional data on the post-COVID period, compare different virus variants, and investigate the correlation between headaches, additional Long-Covid symptoms, and influencing factors.

The main objective of the study was to gather data on the distribution and duration of headaches across different phases. Contrary to our hypothesis, the findings indicate no apparent significant association between the occurrence and duration of headaches as a symptom of Long-Covid and the different virus variants within the four phases. The study suggests that the different phases and variants of SARS-CoV-2 do not play a substantial role in the occurrence or duration of headaches as a symptom of Long-Covid among the participants.

Despite the lack of statistical significance, our study observed a decrease in the number and percentage of participants experiencing headaches from Phase 1 (31.8%) to Phase 4, which could have happened by chance. However, it is important to note that the decrease was not consistently linear across all phases, with a slight decrease in Phase 2 (25.8%), followed by a further decrease in Phase 3 (12.0%), and an increased Phase 4 (14.3%) compared to Phase 3.

According to current literature, Long-Covid has been reported to last from 4 to 12 weeks, with a prevalence ranging from 14.5% to 18.1%, and a duration of longer than 12 weeks affecting 7.8% to 17.0% (56). In our study, participants were less frequently affected for a period of 4 to 12 weeks per phase (4.8%), which does not align with the findings reported in the literature. However, participants affected for longer than 12 weeks exhibited a prevalence (10.2%) that falls within the range suggested by previous studies.

Regarding the distribution of phases, a similar pattern was observed for the duration of headaches compared to their prevalence, showing a decrease across the phases. While phase 1 and 2 still presented with durations lasting from 4 to 12 or longer than 12 weeks, phase 3 and 4 did not include participants with headache duration longer than 4 weeks. It is worth noting that, according to the data from the RKI, a symptom duration of less than 4 weeks is not described as Long-Covid but rather as the acute post-Covid period (40). However, Long-Covid and the acute post-Covid period are often used interchangeably, and it would be essential for further research to have a more precise definition for better differentiation of Long-Covid, its phases, and headaches.

Regarding gender differences, Long-Covid headache affected women slightly more often (29.9%) compared to men (18.8%). However, it is important to mention that the duration of headache did not vary between male and female individuals, although further research is needed to identify possible differences in headache patterns.

Furthermore, when focusing on statistical significance, the survey indicated that gender does not influence the occurrence of headache in terms of prevalence and duration, although females show a trend to have a higher prevalence of headache (57).

In contrast to gender, age played a significant role in the risk of experiencing headaches as a symptom of Long Covid. The study observed that participants who had headaches tended to be younger on average compared to those without headaches. This indicates that younger individuals have a higher likelihood of developing headaches as a symptom of Long Covid. However, it's important to note that age alone is not the sole determining factor for the occurrence of headaches. Other variables and factors, such as individual health conditions, comorbidities, and the overall severity of the Long Covid condition, may also contribute to the presence of headaches.

The study also investigated the association between headache and preexisting headache as a comorbidity. The results showed a significant association, indicating that individuals with preexisting headaches were more likely to experience headaches as a symptom of Long-Covid. The survey findings suggest that preexisting headache conditions may influence the development of headaches in the context of COVID-19 infection.

It is important to note that our study did not collect data on whether the headache occurring post-infection is new and COVID-related or a worsened primary headache from before the infection. Both can be associated with a SARS-CoV-2 infection (54).

It is worth mentioning the lack of association between headache and smoking or headache and alcohol consumption. This study did not find a connection between smoking or alcohol consumption and an increased prevalence of Long-Covid headache. Therefore, smoking and alcohol consumption may not have a substantial impact on the occurrence of headaches. However, further research is needed to investigate the potential influence of the amount of alcohol and smoking on headaches, as our study did not include this information.

In contrast to the literature, and although most of the participants were unvaccinated, our study did not show an association between the occurrence of Long-Covid headache and the type and presence of immunity either via vaccination or naturally acquired (5).

Therefore, vaccination does not decrease the risk of developing Long-Covid headache. Further research is needed to specify the effectiveness of vaccination in reducing Long-Covid symptoms, as our study only focused on its possible association with headache.

When comparing headache with the presence and simultaneous appearance of other Long-Covid symptoms, the study focused on the comparison with other common presentations, including anosmia, fatigue, and tiredness.

Although all three symptoms commonly occur simultaneously with headache, current literature implies anosmia as the most common symptom occurring with headache (54). However, our study revealed that anosmia is less common than tiredness and fatigue. Instead, fatigue occurred most often concurrently with headache, followed by tiredness.

However, there was a significant association between all three symptoms and headache, indicating that individuals with headaches were more likely to experience fatigue, tiredness, and anosmia as well.

By proving a possible relationship between headache and fatigue/tiredness, our study encourages the necessity for further research regarding a possible relationship between headache, fatigue, and tiredness with encephalomyelitis/chronic fatigue syndrome (ME/CFS), which has been suggested to be associated with SARS-CoV-2 (58).

In conclusion, these findings emphasize the interconnectedness of symptoms in Long-Covid, suggesting a potential shared underlying mechanism and the need for holistic approaches in the management and treatment of these conditions.

5.2 Confounding Factors and Limitations

With the help of our cross-sectional survey, the study acquired valuable knowledge about the prevalence and characteristics of Long-Covid headache. However, it is crucial to acknowledge the limitations inherent in our study design as they can significantly impact the interpretation and generalizability of our findings.

Regarding possible recall bias, the study faced two problems. First, there were certain discrepancies between survey participants and non-respondents in relation to age and immunization status. This disparity may introduce bias and impact the generalizability of our results. Second, recall bias may have occurred due to the long period between SARS-CoV-2 infection and survey participation. With periods of up to two years, there might have been an incorrect reevaluation of symptoms and their duration, leading to invalid survey participation and data collection.

Apart from recall bias, certain factors were missing from the data assessment. The study did not encompass factors such as participants younger than 18, ethnicity, or severity of the previous COVID infection, which may limit the comprehensiveness and understanding of Long-Covid.

In terms of representativeness, the study faced limitations due to the relatively low response rate of 14.3%. The division of the sample into smaller subgroups in terms of duration, phases, and symptom relations further reduced the representativeness of our findings, potentially leading to a loss of statistical significance.

The high heterogeneity among studies posed a challenge when comparing our study with others. Variations in study designs, settings, populations, follow-up time, and methods of symptom ascertainment introduced significant differences, making direct comparisons difficult.

Due to the unclear or even absence of standardized definitions of Long-Covid symptoms, the study faced limitations in establishing criteria for identification and understanding of Long-Covid. This was primarily influenced by terminology inconsistency, varying timeframes for symptom duration, and tremendous differences in Long-Covid categorization across the literature.

Because our study acquired data via a survey questionnaire, the information provided by the participants relied solely on subjective interpretation and self-reporting of symptoms, rather than on clear diagnostics in the form of clinical tests. It was particularly challenging to assess the subjective differentiation between Long-Covid headache being related to, already present but worsened by, or independent from SARS-CoV-2. Consequently, this introduced limitations in the accuracy and reliability of the collected data.

The classification and allocation of participants to the four phases and VOCs were based on epidemiological occurrence and the timeframe classification from the RKI. This lack of individual genetic sequencing of RT-PCR results might result in a lack of precision regarding participant association with the phases due to the common overlapping of the VOCs.

Additionally, the worldwide occurrence and epidemiological data of variants of concern exhibited significant variability, limiting the interpretation of our results to the influence of Long-Covid in Bavaria, Germany.

Since our study acquired data via a survey questionnaire, the information provided by the participants relied solely on subjective interpretation and self-reporting of symptoms, rather than on clear diagnostics in the form of clinical tests.

It was particularly challenging to assess the subjective differentiation between Long-Covid headache being related to, already present but worsened by, or independent from SARS-CoV-2. Consequently, this introduced limitations in the accuracy and reliability of the collected data.

The records concerning the effects of immunization did not include the vaccine type or their varying effectiveness against the different VOCs, nor did we differentiate between immunization by vaccination or acquired immunity by infection. Taking this into account, they have the potential to complicate the analysis of symptoms and their correlation with immunization.

Considering these limitations, our study did gain valuable data and insights into the duration and presentation of Long-Covid, its influencing factors, and its specific headache presentation. Nevertheless, larger prospective research is required to overcome these limitations and further support our study's findings.

6. CONCLUSION

Our study provided valuable insights into the prevalence and characteristics of headache as a symptom of Long-Covid. The findings suggest that headache is a common symptom among former SARS-CoV-2 hospitalized patients and is associated with tiredness, fatigue, preexisting headache, and anosmia. However, the hypothesis that headache presents differently in terms of prevalence and duration across the different phases/variants of SARS-CoV-2 has been proven false. Instead, Long-Covid headache appears to be more influenced by simultaneous occurrences of other Long-Covid manifestations and individual patient factors. The study highlights the importance of considering the interconnectedness of symptoms, comorbidities, and influencing factors in understanding and managing Long-Covid. Nevertheless, further research is needed to explore the underlying mechanisms and potential management strategies for Long-Covid, especially regarding headache.

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8. SUMMARY

Objectives: The objective of this study was to collect new data on the post-COVID period, with a specific focus on headaches, including their symptom prevalence, duration, and influencing factors, while comparing different virus variants. the analysis aimed to explore potential associations between its variables, particularly paying attention to smoking/alcohol consumption, gender, age, preexisting headache, immune status, and other Long-COVID symptoms. The study was conducted under the hypothesis that the prevalence and duration of headaches as a post-COVID-19 symptom vary between different variants of SARS-CoV-2.

Material and Methods: The study was designed as a retrospective cross-sectional survey conducted in the rural region of Coburg, Bavaria, Germany, including the REGIOMED Hospital. Data was collected from anonymized sources and categorized into four groups based on different phases of the COVID-19 pandemic, including the SARS-CoV-2 wild type, alpha, delta, and Omicron variants. From a total of 1025 former SARS-CoV-2 hospitalized patients, administered from March 2020 to March 2022, 147 participated in the study through an online questionnaire from September to December 2022. The survey data was combined with information obtained from the hospital's information system, Orbis. The survey collected various variables related to Long-Covid, with a specific focus on headache and headache-related factors, such as gender, smoking/alcohol consumption, immune status, pre-existing health conditions, and Long-Covid symptoms. Statistical analysis was performed using Stata 16 Statistics, including descriptive statistics, the Mann-Whitney U test, the chi-squared test, and Fisher's exact test. The significance level (p-value) was set at <0.05 to assess the significance of the results.

Results: The study presented no significant difference in gender distribution across the different phases, as well as no significant association between gender and the occurrence of headaches. However, age was found to be associated with survey response, with respondents tending to be slightly younger compared to non-respondents. With a headache occurrence of 23.81%, there was no significant association between headache prevalence and the different phases of the study. The duration of headaches varied, with individuals experiencing headache for less than 4 weeks (8.8%), 4 to 12 weeks (4.8%), and longer than 12 weeks (10.2%). Nevertheless, no significant association between headache duration and the different phases was found. Headache was found to be significantly associated with tiredness and fatigue, indicating that individuals with headache were more likely to also report feeling tired or fatigued.

The study also examined the relationship between preexisting headache and Long-Covid headache, presenting a significant relation. Participants with preexisting headache were more likely to experience headache as Long-Covid symptom. Anosmia, fatigue, and tiredness also were significantly associated with headache, characterized by an increased likelihood of individuals presenting with headaches simultaneously experiencing one or more of those symptoms. No significant associations were found between headache and smoking/alcohol consumption or headache and the participant´s immune status.

Conclusion: The study suggests headache as a common symptom among former SARS-CoV-2 hospitalized patients, being associated with tiredness, fatigue, preexisting headache, and anosmia. However, the hypothesis that headache presents differently in terms of prevalence and duration across the different phases/variants of SARS-CoV-2 has been proven false. Instead, Long-Covid headache appears to be more influenced by simultaneous occurrences of other Long-Covid manifestations and individual patient factors. The study highlights the importance of considering the interconnectedness of symptoms, comorbidities, and influencing factors in understanding and managing Long-Covid. Nevertheless, further research is needed to explore the underlying mechanisms and potential management strategies for Long-Covid, especially regarding headache.

9. CROATIAN SUMMARY

Ciljevi: Cilj ovog istraživanja bio je prikupiti nove podatke o post-COVID razdoblju, s posebnim fokusom na glavobolje, uključujući njihovu prevalenciju simptoma, trajanje i faktore koji ih utječu, te usporediti različite varijante virusa. Analiza je imala za cilj istražiti moguće povezanosti između varijabli, posebno s naglaskom na pušenje/konzumaciju alkohola, spol, dob, postojeće glavobolje, imunološki status i druge simptome dugotrajne COVID infekcije. Istraživanje je provedeno na temelju hipoteze da prevalencija i trajanje glavobolja kao simptoma post-COVID-19 variraju između različitih varijanti SARS-CoV-2.

Materijal i metode: Istraživanje je dizajnirano kao retrospektivna presječna studija provedena u ruralnoj regiji Coburg, Bavarska, Njemačka, uključujući bolnicu REGIOMED. Podaci su prikupljeni iz anonimiziranih izvora i kategorizirani su u četiri grupe na temelju različitih faza COVID-19 pandemije, uključujući divlji tip SARS-CoV-2, alfa, delta i omikron varijante. Od ukupno 1025 bivših pacijenata hospitaliziranih zbog SARS-CoV-2, tijekom razdoblja od ožujka 2020. do ožujka 2022., 147 sudionika je sudjelovalo u istraživanju putem online upitnika od rujna do prosinca 2022. Podaci iz ankete su kombinirani s informacijama dobivenim iz informacijskog sustava bolnice, Orbis. Anketa je prikupila razne varijable povezane s dugotrajnim COVID-om, s posebnim fokusom na glavobolju i faktore povezane s glavoboljom, poput spola, pušenja/konzumacije alkohola, imunološkog statusa, postojećih zdravstvenih stanja i simptoma dugotrajne COVID infekcije. Statistička analiza provedena je koristeći SPSS Statistics, uključujući deskriptivnu statistiku, Mann-Whitney U test, chi-kvadrat test i Fisherov točan test. Razina značajnosti (p-vrijednost) postavljena je na <0,05 kako bi se procijenila važnost rezultata.

Rezultati: Studija nije pokazala značajnu razliku u raspodjeli spola između različitih faza, kao ni značajnu povezanost između spola i pojave glavobolje. Međutim, dob je utvrđena kao povezana s odgovorom na anketu, s ispitanicima koji su bili nešto mlađi u usporedbi s onima koji nisu odgovorili. S prevalencijom glavobolje od 23,81%, nije utvrđena značajna povezanost između prevalencije glavobolje i različitih faza istraživanja. Trajanje glavobolja variralo je, pri čemu su osobe imale glavobolju kraće od 4 tjedna (8,8%), od 4 do 12 tjedana (4,8%) i duže od 12 tjedana (10,2%). Međutim, nije utvrđena značajna povezanost između trajanja glavobolje i različitih faza. Glavobolja je pokazala značajnu povezanost s osjećajem umora i iscrpljenosti, što ukazuje da su osobe s glavoboljom vjerojatnije izvijestile i o osjećaju umora ili iscrpljenosti.

Studija je također istražila odnos između postojeće glavobolje i glavobolje povezane s dugotrajnim COVID-om, prikazujući značajnu povezanost. Sudionici s postojećom glavoboljom bili su skloniji doživjeti glavobolju kao simptom dugotrajne COVID infekcije. Anozmija, umor i iscrpljenost također su bili značajno povezani s glavoboljom, što ukazuje na povećanu vjerojatnost da osobe s glavoboljom također doživljavaju jedan ili više tih simptoma istovremeno. Nisu pronađene značajne povezanosti između glavobolje i pušenja/konzumacije alkohola ili glavobolje i imunološkog statusa sudionika.

Zaključak: Studija sugerira glavobolju kao čest simptom među bivšim pacijentima hospitaliziranima zbog SARS-CoV-2, povezan s umorom, iscrpljenošću, prethodnom glavoboljom i anosmijom. Međutim, hipoteza da se glavobolja razlikuje u smislu prevalencije i trajanja u različitim fazama/varijantama SARS-CoV-2 pokazala se netočnom. Umjesto toga, glavobolja povezana s dugotrajnim COVID-om čini se više utjecana istovremenim pojavama drugih manifestacija dugotrajnog COVID-a i individualnim čimbenicima pacijenta. Studija ističe važnost razmatranja međusobne povezanosti simptoma, komorbiditeta i faktora koji utječu na razumijevanje i upravljanje dugotrajnim COVID-om. Ipak, potrebna su daljnja istraživanja radi istraživanja temeljnih mehanizama i potencijalnih strategija upravljanja dugotrajnim COVID-om, posebno u vezi s glavoboljom.