Retrospective analysis of hospitalized patients, comparing different SARS-CoV-2 variants regarding anosmia

Heinig, Silvio

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Silvio Achim Heinig

RETROSPECTIVE ANALYSIS OF HOSPITALIZED PATIENTS, COMPARING DIFFERENT SARS-COV-2 VARIANTS REGARDING ANOSMIA

Diploma Thesis

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LIST OF ABBREVIATIONS

ACE2 – Angiotensin converting enzyme 2

ARDS – Acute respiratory distress syndrome

BMI – Body mass index

CBC – Complete blood count

CRP – C-reactive Protein

CT – Computed tomography

DAD – Diffuse alveolar damage

ECG – Electrocardiogram

ICU – Intensive care unit

IL-1 – Interleukin 1

IL-6 – Interleukin 6

LDH – Lactate dehydrogenase

NAAT – Nucleic acid amplification test

ORN – Olfactory receptor neurons

PASC – Postacute sequelae of SARS-CoV-2 infection

PHEIC – Public health emergency of international concern

PT – Prothrombin time

PPT – Partial thromboplastin time

RBD – Receptor binding domain

RKI – Robert Koch Institut

RT-qPCR - Reverse transcriptase real-time polymerase chain reaction

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

S Protein – Spike protein

TNF-alpha – Tumor necrosis factor-alpha

USA – United States of America

VOC – Variant of concern

VOI – Variant of interest

WHO – World Health Organization

1. INTRODUCTION

1.1 Coronavirus disease 2019 (COVID-19)

1.1.1 Epidemiology

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had a profound impact on global health, economies, and societies since its emergence in late 2019. This short introduction provides an overview of the epidemiology of COVID-19, including its global spread and the situation in Germany.

The first known cases of COVID-19 were reported in December 2019. in Wuhan, Hubei Province, China (1). The virus quickly spread within China and later reached various countries worldwide through international travel. On March 11, 2020. the World Health Organization (WHO) declared COVID-19 a pandemic, acknowledging its global reach and impact (2).

Germany reported its first confirmed case of COVID-19 on January 28, 2020. The individual was a 33-year-old man from Bavaria who had contracted the virus during a business trip to China (3). This marked the beginning of COVID-19 transmission within the country.

In response to the increasing number of cases, the German government implemented several measures to contain the virus's spread. These included extensive testing, contact tracing, social distancing guidelines, and lockdowns. The Robert Koch Institute (RKI), Germany's federal agency responsible for disease control and prevention, played a crucial role in monitoring the situation and providing recommendations.

As of June 2023., Germany had reported over 38.4 million confirmed COVID-19 cases, with varying case rates across different regions. Sadly, these cases resulted in 174.352 deaths in relation to the virus (4). Based on a population of 83.1 million inhabitants, this corresponds to an overall infection rate of 46.2% and a total mortality rate of 0.5% (5).

In Germany, a total of 64.877,038 COVID-19 initial vaccinations have been administered as of June 13, 2023. This corresponds to a vaccination rate of at least once vaccinated individuals of 78.0%. Fully immunized are 76.4% of the population. A booster vaccination has been received by 62.7%. Already double boosted are 15.2% of the population (5).

Due to the continuously decreasing virulence of the SARS-CoV-2, the WHO Director-General determined on May 5, 2023. that COVID-19 has transitioned into a persistent health challenge, no longer classified as a public health emergency of international concern (PHEIC) (6).

1.1.2 Etiology and transmission

SARS-CoV-2 belongs to the family of β-coronaviruses and is characterized as an enveloped, non-segmented, positive-sense, single-stranded RNA virus. Its genome encodes several proteins, including four structural proteins: spike, envelope, membrane, and nucleocapsid. The spike (S) protein plays a vital role in facilitating viral entry by binding to the ACE2 receptor on the surface of host cells. The envelope (E) and membrane (M) proteins contribute to the structure of the viral envelope, while the nucleocapsid (N) protein packages the viral RNA genome into a helical ribonucleocapsid (7). Additionally, the viral genome encodes 16 nonstructural proteins, which are involved in forming the replicase-transcriptase complex essential for viral replication (8).

The exact origin and initial transmission events are still under investigation, but zoonotic transmission from animals, possibly originating from a seafood market in Wuhan, is suspected (2). Like SARS-CoV and MERS-CoV, it is likely that bats serve as the original species for SARS-CoV-2 due to its 96% whole-genome similarity with a bat coronavirus called BatCoV RaTG13, originating from Yunnan Province (9).

However, like SARS-CoV and MERS-CoV, which typically require intermediate hosts before infecting humans (10), it is probable that SARS-CoV-2 was transmitted to humans through other animal species.

Transmission of COVID-19 occurs through various modes. The primary modes of transmission involve direct exposure to respiratory fluids, either through inhalation of droplets or aerosol particles (11). Droplets are larger respiratory particles that can travel short distances before falling to the ground, while aerosols are smaller particles that can remain suspended in the air for extended periods of time. The concentration of aerosol particles is typically highest within a range of 3 to 6 feet from the infectious source (12).

In poorly ventilated areas, the risk of transmission through airborne particles may be increased, as the particles can linger in the air for minutes to hours, potentially exposing individuals in close proximity (12).

While indirect fomite transmission, which involves the transfer of the virus through contaminated surfaces or objects, is possible, it is considered unlikely to be a major mode of transmission (13).

Vertical transmission of SARS-CoV-2 is possible, but it appears to be relatively rare. A systematic review and meta-analysis by Kotlyar *et al*. showed, that in cases where pregnant women in their 3rd trimester were tested positive for COVID-19, the transmission of the virus to the fetus or newborn occurred in only 3.2% of 936 tested neonates (14).

1.1.3 Clinical presentation

COVID-19 exhibits a wide range of clinical manifestations, spanning from asymptomatic infection to critical and fatal illness. While the exact proportion of asymptomatic cases is uncertain, it is estimated that up to 40 percent of infections may be asymptomatic (15). Most symptomatic infections present with mild symptoms, but severe disease, characterized by hypoxia and pneumonia, has been reported in 15 to 20 percent of cases (16). Severe disease can affect individuals of any age, but is more common in adults with advanced age or underlying medical comorbidities (17).

The incubation period of COVID-19, from exposure to symptom onset, typically ranges from three to five days, although it can extend up to 14 days (18,19). The initial presentation of COVID-19 is often characterized by cough, myalgias, and headache. Other reported symptoms include diarrhea, sore throat, and abnormalities in smell or taste (19,20).
The predominant serious manifestation of COVID-19 is pneumonia, which is characterized by fever, cough, dyspnea, and the presence of bilateral pulmonary infiltrates (21). Since the emergence of variant strains such as Delta and Omicron, mild upper respiratory symptoms like nasal congestion and sneezing were among the leading symptoms (22).

Laboratory findings can aid in the diagnosis, risk stratification, and management of COVID-19 patients. Severe disease is often accompanied by elevated inflammatory markers such as C-reactive protein (CRP), ferritin, interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) (23,24). Additionally, higher levels of D-dimer, have been linked to poorer outcomes. Studies have shown that non-survivors of COVID-19 tend to experience a gradual decrease in lymphocyte count and an increase in D-dimer levels in the course of their disease (25).

Acute respiratory distress syndrome (ARDS) is a major complication seen in severe cases, often occurring shortly after the onset of dyspnea. Mechanical ventilation has been necessary in 12 to 24 percent of hospitalized patients according to large studies conducted in the USA (26,27). Other complications include thromboembolic events, acute cardiac injury, kidney injury, and inflammatory complications (20).

Persistent symptoms following acute COVID-19, known as "Long COVID" (28), are discussed in more detail in Chapter 1.2.

1.1.4 Diagnostic methods

Early detection and reliable testing for COVID-19 is very important, as this can break chains of infection and thus reduce the spread at an early stage (29). Various tests are available for this purpose. The use of a specific method depends on its sensitivity and specificity, turnaround time for results, time of suspected exposure, staff availability, costs, and infrastructure. These methods can be broadly categorized into two main approaches: molecular testing and serological testing.

Molecular testing by a nucleic acid amplification test (NAAT), such as reverse transcriptase real-time polymerase chain reaction (RT-qPCR), is the preferred method for early detection, even before an individual develops symptoms. RT-qPCR, targeting various genes of the SARS-CoV-2 genome, is considered the gold standard for COVID-19 diagnosis (30,31). The WHO recommends the *E* gene as the initial screening target, followed by confirmation with the RdRp gene (30). Despite the complexity and expense of these nucleic acid-based techniques, they provide high sensitivity and specificity (32). A Meta-analysis by Böger *et al.* showed that samples from sputum (97.2%, 95% CI 90.3%-99.7%), nasopharyngeal/throat swab (73.3%, 95% CI 68.1%-78.0%), and saliva (62.3%, 95% CI 54.5%-69.6%) were the most sensitive in detecting COVID-19 (33). It is worth mentioning for RT-qPCR that even 90 days post-infection, detectable RNA and thus a positive test result can still occur (34).

Antigen testing offers rapid and accessible detection of SARS-CoV-2, providing faster and cheaper results compared to NAATs. However, antigen tests are generally less sensitive than NAATs. They can be particularly useful in symptomatic individuals within the first five to seven days of symptoms when viral replication is at its highest. Subsequent repeated tests may also increase sensitivity (35). A positive antigen test in symptomatic individuals indicates SARS-CoV-2 infection, while a negative result should be followed by additional testing. In asymptomatic individuals following exposure, a negative antigen test should generally be followed by further testing (34). Antigen testing can be employed for screening purposes, such as in outbreak settings and repeated screening of high-risk individuals. Antigen tests exhibit high specificity, but their sensitivity varies depending on the time of testing, symptomatic status, and viral load. The reliability of antigen tests can vary among different brands and models (36).

Serological testing detects the presence of antibodies produced by the immune system in response to SARS-CoV-2 infection. These tests are primarily used to determine past infections and assess population-level exposure to the virus. Serological tests are performed on blood samples and can help identify individuals who have developed an immune response to

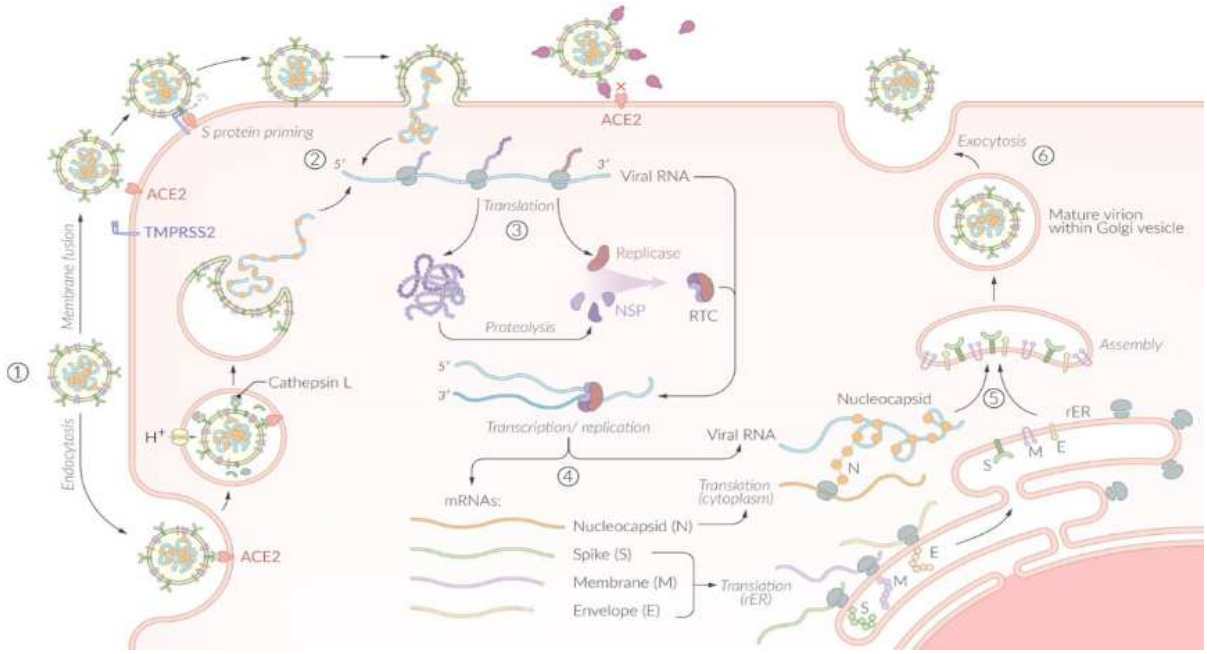
the virus. However, antibody tests are not suitable for diagnosing acute infections as it takes time for the body to produce detectable levels of antibodies (37–39).

Diagnostic testing with chest CT, although having a sensitivity of 94.6% (95% CI: 91.9%, 96.4%), should be followed by molecular testing due to its low specificity of 46.0% (95% CI: 31.9%, 60.7%) (40).

1.1.5 Viral life cycle and pathophysiology

As mentioned before, SARS-CoV-2 is primarily transmitted through respiratory droplets and aerosols from person to person (11). The virus enters the body through the binding of its S protein to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells **(Figure 1)**. The S protein consists of two subunits: S1, responsible for host cell receptor binding, and S2, involved in membrane fusion (41). After the S protein binds to ACE2, it undergoes cleavage by transmembrane protease serine 2 (TMPRSS2), leading to conformational changes, which activates viral and host cell membrane fusion. This enables the virus to enter host cells through endocytosis or membrane fusion (42). The virus has a predilection for pulmonary alveolar epithelial cells because of their high expression of ACE2 receptors (43). After fusion of the membranes, the viral RNA undergoes transcription by RNA polymerase, resulting in the formation of negative-sense viral RNA. This negative-sense RNA serves as a template for the production of new strands of positive-sense viral RNA, which are used to synthesize viral proteins in the cell cytoplasm (44,45). The nucleocapsid (N) protein binds to the newly formed genomic RNA, and the membrane (M) protein facilitates integration into the cellular endoplasmic reticulum. Nucleocapsids are enclosed in the endoplasmic reticulum membrane, transported to the cell membrane via Golgi vesicles, and released into the extracellular space through exocytosis. This process ensures the survival and replication of the virus within an organism and is also the foundation of viral transmission (41).

Figure 1. Viral life cycle of SARS-CoV-2 (46).



The pathophysiology of COVID-19 involves not only the direct effects of the virus on the respiratory system but also a dysregulated immune response triggered by the infection (47,48).

The course of the infection typically begins with an asymptomatic phase. During this asymptomatic phase, the virus binds to ACE2 receptors of nasal epithelial cells in the upper respiratory tract. At this point there is little or no symptoms due to delayed and still weakened immune response, but at the same time there is high contagiousness (49).

As the virus migrates to the upper respiratory tract, symptoms such as fever, malaise, and dry cough may occur. The immune response intensifies, characterized by the release of cytokines and interferons. If the immune response of the host is sufficient to contain the infection, there is usually no progression from this stage (49).

Nevertheless, approximately one-fifth of infected patients progress to the involvement of the lower respiratory tract, where the virus invades type 2 alveolar epithelial cells. Replication occurs, leading to the release of various cytokines and inflammatory markers like IL-1, IL-6 and TNF-alpha , resulting in a "cytokine storm" (50). This storm attracts neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, leading to lung inflammation and injury. The host cells undergo apoptosis, releasing new viral particles that infect adjacent cells, perpetuating the cycle of infection and inflammation. Ultimately, diffuse alveolar damage occurs, culminating in acute respiratory distress syndrome (ARDS) (51).

1.1.6 Acute respiratory distress syndrome

The key features of ARDS include the rapid onset of respiratory distress, severe impairment of gas exchange, and diffuse damage to the alveolar-capillary membrane in the lungs. The syndrome is associated with high morbidity and mortality rates, often requiring mechanical ventilation and intensive care support. ARDS as a clinical syndrome is defined by the presence of hypoxemia, and bilateral pulmonary infiltrates on chest imaging that cannot be fully explained by heart failure or fluid overload. ARDS typically occurs as a result of underlying lung injury caused by various factors such as pneumonia, sepsis, trauma, aspiration, or other inflammatory conditions (52,53).

ARDS begins with tissue damage caused by pulmonary or extrapulmonary insults, triggering the release of inflammatory mediators such as IL-1. This sets off an inflammatory reaction, leading to the migration of neutrophils into the alveoli (54,55).

Excessive release of neutrophilic mediators, including cytokines, proteases, and reactive oxygen species, damages the alveolar capillaries and endothelial cells, resulting in diffuse alveolar damage (DAD). During the exudative phase, fluid accumulates in the interstitium and on the alveolar surface, causing pulmonary edema. Pulmonary capillary wedge pressure is not elevated, distinguishing ARDS from cardiogenic pulmonary edema. Accumulation of fluid impairs lung compliance, leading to respiratory distress (54,55).

In the further course, hyaline membranes form in the alveolar space due to the exudation of neutrophils and protein-rich fluid. These membranes impair gas exchange, contributing to hypoxemia. Hypoxemia triggers compensatory hyperventilation, resulting in respiratory alkalosis. Chronic hypoxic pulmonary vasoconstriction also occurs, leading to pulmonary hypertension and the development of a right-to-left shunt, exacerbating hypoxemia. Direct damage to type I and type II pneumocytes leads to a decrease in surfactant production and release, causing alveolar collapse and worsens intrapulmonary shunting and hypoxemia (54,55).

In the late stage of ARDS, there is an organizing phase characterized by the proliferation of type II pneumocytes and infiltration of fibroblasts. According to a meta-analysis by Hama Amin *et al.*, approximately 45% of those who survived COVID-19 appeared to have remodeling of lung tissue and progressive pulmonary fibrosis (56). If multiorgan failure occurred simultaneous to ARDS, mortality rates were up to 50% (57).

Mechanical ventilation in ARDS can be another contributor to lung injury and inflammation. High volumes and pressures during ventilation can worsen lung damage, commonly known as ventilator-induced lung injury. Overdistension (volutrauma) and elevated

pressures (barotrauma) affect lung compliance. Cyclic stretching of lung cells also activates proinflammatory pathways, leading to cytokine release and cell damage. Atelectrauma, caused by repetitive opening and closing of alveoli puts further strain on the lungs (54).

1.1.7 Prevention and vaccination

Preventive measures are crucial in controlling the spread of SARS-CoV-2. In healthcare settings, where community transmission is widespread, preventive strategies for all individuals are necessary to reduce the risk of exposures. Personal preventive measures include hand washing, respiratory hygiene, and the use of hand sanitizer with at least 60% alcohol. Adequate ventilation of indoor spaces, staying home and getting tested when symptoms occur, avoiding close contact with individuals who have or may have COVID-19, and wearing masks are also important preventive measures. N95 and K95 masks offer greater protection compared to surgical masks, while cloth masks provide the least protection. Additional measures, like repeated testing, are recommended for patients with suspected or confirmed COVID-19 (58).

Many governments around the world have imposed social distancing, quarantines, and even large-scale lockdowns in the interests of public health. The effectiveness and adequacy of these individual measures are still under retrospective evaluation. Lockdowns in particular seem to have an alarming impact on children’s mental and physical health and development (59,60).

Vaccines have played a crucial role in preventing the spread of COVID-19. There are several types of COVID-19 vaccines, including mRNA vaccines, vector-based vaccines, and protein subunit vaccines.

mRNA vaccines, like the Pfizer-BioNTech and Moderna vaccines, use a small piece of the virus's mRNA to instruct the host's cells to produce the viral spike protein. This protein triggers an immune response, leading to the production of antibodies and memory cells.

Vector-based vaccines, such as the Johnson & Johnson and AstraZeneca vaccines, use another virus, e.g., Adenovirus, as a vector to deliver a modified version of the spike protein found on SARS-CoV-2. The spike protein stimulates an immune response with a similar mechanism seen in mRNA vaccines.

In contrast to that, protein subunit vaccines, like the Novavax, contain a spike protein that is produced in vitro by recombinant technology before being injected. (61,62).

In terms of variant-adapted COVID-19 vaccines, bivalent vaccines containing the original and Omicron BA.1 spike mRNA sequences have been approved as boosters. Boosting with the BA.1 bivalent vaccine enhances protection against BA.5 and related subvariants.

Bivalent vaccines with the Omicron BA.5 spike sequence have also been developed and approved as boosters. They are expected to be more effective against BA.4 and BA.5 subvariants. Other variant-adapted vaccines, such as the Alpha/Beta bivalent vaccine, are currently being evaluated (63).

Zeng *et al.* conducted a comprehensive analysis on the effectiveness of COVID-19 vaccines against different variants. The analysis included 11 randomized controlled trials, 20 cohort studies, and 26 case-control studies, with a total of over 161 million participants and eleven vaccines were examined. The results showed that full vaccination was highly effective against the Alpha variant, with a vaccine effectiveness (VE) of 88.0%. It was moderately effective against the Beta, Gamma, and Delta variants, with VE values of 73.0%, 63.0%, and 77.8% respectively. For the Omicron variant, full vaccination had a VE of 55.9%. However, booster vaccination significantly improved the effectiveness against the Delta and Omicron variants, with VE values of 95.5% and 80.8% respectively. mRNA vaccines, such as the Moderna and the BioNTech/Pfizer vaccines, demonstrated higher VE against all variants compared to other vaccine types. There were significant interactions between VE and vaccine type, indicating that mRNA vaccines had a stronger protective effect against the Alpha, Beta, Gamma, and Delta variants (64).

1.1.8 Management of hospitalized patients with COVID-19 infection

During the assessment of patients admitted to the hospital with confirmed or suspected COVID-19, it is important to examine for indicators linked to severe illness. This evaluation aims to identify any organ dysfunction or existing medical conditions that might complicate the clinical course of the disease. Several laboratory studies are conducted initially. These include a complete blood count (CBC) with a focus on the trend of total lymphocyte count, and a basic metabolic panel. For patients with severe COVID-19 or those in need of oxygen or ventilatory support, additional tests such as CRP, lactate dehydrogenase (LDH), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, D-dimer, troponin, and electrocardiogram (ECG) are performed. Chest x-rays are used for evaluating pulmonary complications, and chest CT scans are reserved for cases that could significantly impact clinical management. Routine echocardiograms are not performed for COVID-19 patients, but they may be considered if there are indications of myocardial injury or cardiovascular findings suggestive of cardiomyopathy. If secondary bacterial infection is suspected, blood cultures, sputum Gram stain, and culture are checked, along with procalcitonin levels to assess the risk. However, the specificity of procalcitonin decreases as the disease progresses (19,23,25,65).

According to the National Institute of Health (NIH) guidelines **(Table 1)** for therapeutic management of hospitalized adults with COVID-19 from April 2023., patients who do not require supplemental oxygen, but are at high risk of progressing to severe disease, should be treated with Remdesivir (66). Remdesivir is an adenosine nucleotide analogue that inhibits RNA replicase and therefore decreases RNA synthesis of SARS-CoV-2 (67). Administration for a duration of 5 days is advised but there is insufficient evidence for Remdesivir to be recommended or withheld in this patient group (68–70).

For patients who require conventional oxygen, the management recommendations vary based on the severity and oxygen requirements. In patients who only require minimal conventional oxygen, the guideline recommends using Remdesivir without Dexamethasone. The hyperinflammatory state, which could benefit from corticosteroids, may not yet be fully developed in these patients. Studies, such as the ACTT-1 trial, have shown that Remdesivir significantly reduces the time to clinical recovery and mortality in patients receiving conventional oxygen (69,71). However, for most patients requiring conventional oxygen, the NIH-guideline recommends using Dexamethasone in combination with Remdesivir. The combination of Remdesivir and Dexamethasone has shown improved clinical outcomes in hospitalized COVID-19 patients, reducing the need for mechanical ventilation, the duration of hospitalization and mortality (72,73).

In patients with rapidly increasing oxygen needs and systemic inflammation, adding a second immunomodulatory drug, such as oral Baricitinib or intravenous Tocilizumab, to Dexamethasone is recommended. Large randomized trials have evaluated the use of Dexamethasone in combination with Baricitinib or Tocilizumab, demonstrating benefits in patients who require high-flow nasal cannula oxygen or noninvasive ventilation (74,75).

For COVID-19 patients requiring mechanical ventilation or ECMO, Dexamethasone is recommended along with a second immunomodulator, such as Baricitinib or Tocilizumab. Prophylactic heparin is recommended for VTE prevention, while therapeutic anticoagulation is not advised for critically ill patients, including those on mechanical ventilation or ECMO (76,77).

Table 1. NIH-guideline for therapeutic management of hospitalized patients with COVID-19 (66).

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone** (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] (BIII)	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] (CIIa) For other patients: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[d] (BIIa). If remdesivir cannot be obtained, use **dexamethasone** (BI).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[g] (BIIa) or **IV tocilizumab**[g] (BIIa) to 1 of the options above.	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): • **PO baricitinib**[g] (AI) • **IV tocilizumab**[g] (BIIa) Add **remdesivir** to 1 of the options above in certain patients (CIIa).[i]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (BIII).
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[g] (BIIa) • **IV tocilizumab**[g] (BIIa)	

1.2 Postacute COVID-19 syndrome ("long COVID")

Postacute COVID-19 syndrome, commonly referred to as long COVID, is characterized by the presence of persistent symptoms and health complications that last for more than four weeks after the initial confirmation or suspicion of COVID-19 infection. It encompasses the enduring effects experienced by individuals even after they have recovered from the acute phase of the illness. Long COVID is characterized by a range of physical, cognitive, and psychological symptoms that can significantly impact a person's quality of life. Commonly associated symptoms encompass fatigue, joint and muscle aches, chest pain, palpitations, dyspnea, cognitive impairment, mood changes, headaches, as well as loss of smell and taste (78).

1.2.1 Prevalence of long COVID

The prevalence of postacute COVID-19 symptoms is not yet precisely known, as it seems to vary over the course of the pandemic, depending on the currently prevailing variant of SARS-CoV-2 (79). A comprehensive analysis conducted by O'Mahoney *et al.*, encompassing 194 studies and involving a total of 735.006 participants, revealed that a significant proportion of COVID-19 survivors, regardless of hospitalization status, continued

to experience unresolved symptoms, with up to 45% reporting persistent symptoms during an average follow-up period of 126 days (80).

1.2.2 Risk factors for the development of postacute sequelae of COVID-19

Studies have shown that female patients have a significantly higher risk of developing long COVID. Additionally, age plays a role, with older individuals in the age groups of 40-69 years and ≥70 years facing a greater risk compared to adults younger than 40 years. Body mass index (BMI) is another important factor, as obesity (BMI ≥ 30) has been associated with an increased risk of long COVID. Smoking status also plays a role, with current smokers having a higher risk compared to nonsmokers. Certain comorbidities like anxiety/depression, asthma, chronic obstructive pulmonary disease (COPD), diabetes, immunosuppression, and ischemic heart disease have also been linked to an increased risk for the development of postacute COVID-19 syndrome. The severity of the initial infection is also a prognostic factor. Patients who were hospitalized or required ICU admission during the acute phase of COVID-19 showed increased tendency for postacute sequelae of SARS-CoV-2 (81).

1.2.3 Pathophysiology of long COVID

The exact mechanisms and pathophysiology underlying postacute COVID-19 syndrome are not fully understood. It is believed to involve a complex interplay of persistent inflammation, immune dysregulation, organ damage, and neurological changes triggered by the initial viral infection (82).

One aspect of long COVID involves neurological symptoms that arise from complications such as brain damage, stroke, encephalitis, or Guillain Barré syndrome. The entry of SARS-CoV-2 into the brain can trigger neuroinflammation, sustained neuroinflammatory responses, microthrombosis, and mitochondrial dysfunction. These factors contribute to chronic fatigue, cognitive disorders, and other mental health issues (82).

Persistent cardiac abnormalities can be caused by myocardial injury during the acute infection. The virus infiltrates cardiomyocytes and endothelial cells, resulting in inflammation and dysfunction of the microvasculature. Autoimmune reactions and the development of anti-phospholipid antibodies further contribute to vascular inflammation, thrombotic complications, structural remodeling of the heart, and potential complications such as heart failure, arrhythmia, and vasculitis (82).

Severe respiratory inflammation and injury can lead to lung fibrosis as a long-term complication. Prolonged exposure to supplemental oxygen increases oxidative stress and activates fibrotic pathways. Damage to lung vasculature and microvascular disorders can give rise to pulmonary hypertension and respiratory symptoms. Dysfunctions in the autonomic nervous system can contribute to dyspnea and abnormalities in regulating ventilation (82).

Underlying immune system disorders and sustained dysregulated immune activation also play a role in long COVID. Abnormalities in T-cell function, residual viral proteins in tissues with persistent inflammation, and the development of autoantibodies against immunomodulatory proteins or tissues have been observed (82).

1.2.4 Prevention of postacute COVID-19 syndrome

Based on the available evidence, vaccination plays a role in preventing long COVID. Several studies have indicated that vaccination before acute SARS-CoV-2 infection is associated with reduced risks or odds of long COVID. Receiving two doses seems to be more effective than one dose alone in preventing long COVID. Additionally, studies have investigated the impact of vaccination on individuals who have already experienced COVID-19 and developed long-COVID symptoms. Some of these studies have shown an improvement in long-COVID symptoms after at least one dose of the vaccine, while others have reported no change or worsening of symptoms. The level of evidence supporting these findings is currently low (grade III, case-controls, cohort studies), and more research is needed to further understand the relationship between vaccination and long COVID (83).

Early findings from the Veterans Affairs database indicate that administering Nirmatrelvir-Ritonavir during the initial phase of COVID-19 infection is linked to a 26% decrease in the likelihood of developing long COVID (84). According to Boglione *et al.* the administration of Remdesivir in hospitalized patients with COVID-19 infection resulted in a 35.9% decrease in long COVID during follow-up (85)

1.3 Viral variants of SARS-CoV-2

The COVID-19 pandemic has been shaped by the emergence of various variants of SARS-CoV-2. Some of these variants have raised concerns due to their potential for increased transmissibility, virulence, or reduced vaccine effectiveness. Over time, the virus has undergone genetic mutations, leading to the emergence of different variants, such as the alpha, beta, gamma, delta, and omicron variants. These variants continue to evade natural and vaccine-induced immunity, and efforts are being made to monitor their impact and understand their characteristics (86). The following provides an overview of the characteristics of the major variants of concern (VOC).

1.3.1 Alpha (B.1.1.7 lineage)

The Alpha variant of SARS-CoV-2 was initially identified in the United Kingdom in September 2020. It is characterized by numerous genetic changes, including several amino acid substitutions in the spike protein. These mutations, such as N501Y, have been found to increase the affinity of the virus for the ACE2 receptor. Infections with the Alpha variant were associated with a higher disease severity and increased transmissibility compared to earlier virus strains. The spike protein is crucial for neutralizing antibody efficacy, and these genetic variations seem to impact the effectiveness of vaccines. A sublineage with the E484K mutation is thought to make the virus less susceptible to these neutralizing antibodies and potentially reduce the efficacy of vaccines (87–89).

1.3.2 Beta (B.1.351 lineage)

In December 2020, a new variant known as Beta B.1.351 was first reported in South Africa. The spike protein of the B.1.351 variant contains nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V), with three of these mutations (K417N, E484K, and N501Y) located in the receptor-binding domain (RBD), resulting in enhanced binding affinity for ACE receptors. These mutations have been linked to a higher contagiousness and decreased efficacy of monoclonal antibody therapy and decreased neutralization by antibodies (90,91).

1.3.3 Gamma (P.1 lineage)

The Gamma variant of SARS-CoV-2, also known as lineage P.1, was first detected in Tokyo on January 6, 2021. It originated from travelers arriving from the Brazilian Amazonas state. This variant exhibits several S-protein polymorphisms, including L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F. In specific RBD key positions (K417N, E484K, N501Y), it shares similarities with the Beta (B.1.351) variant. The Gamma variant is also associated with increased transmissibility, reduced effectiveness of neutralizing antibodies, and potentially increased disease severity. In Germany, the combined proportion of Beta and Gamma in the overall prevalence of the COVID-19 variants never exceeded 5% over the entire course, which gave them a subordinate role in the pandemic situation in Germany. (92–94).

1.3.4 Delta (B.1.617.2 lineage)

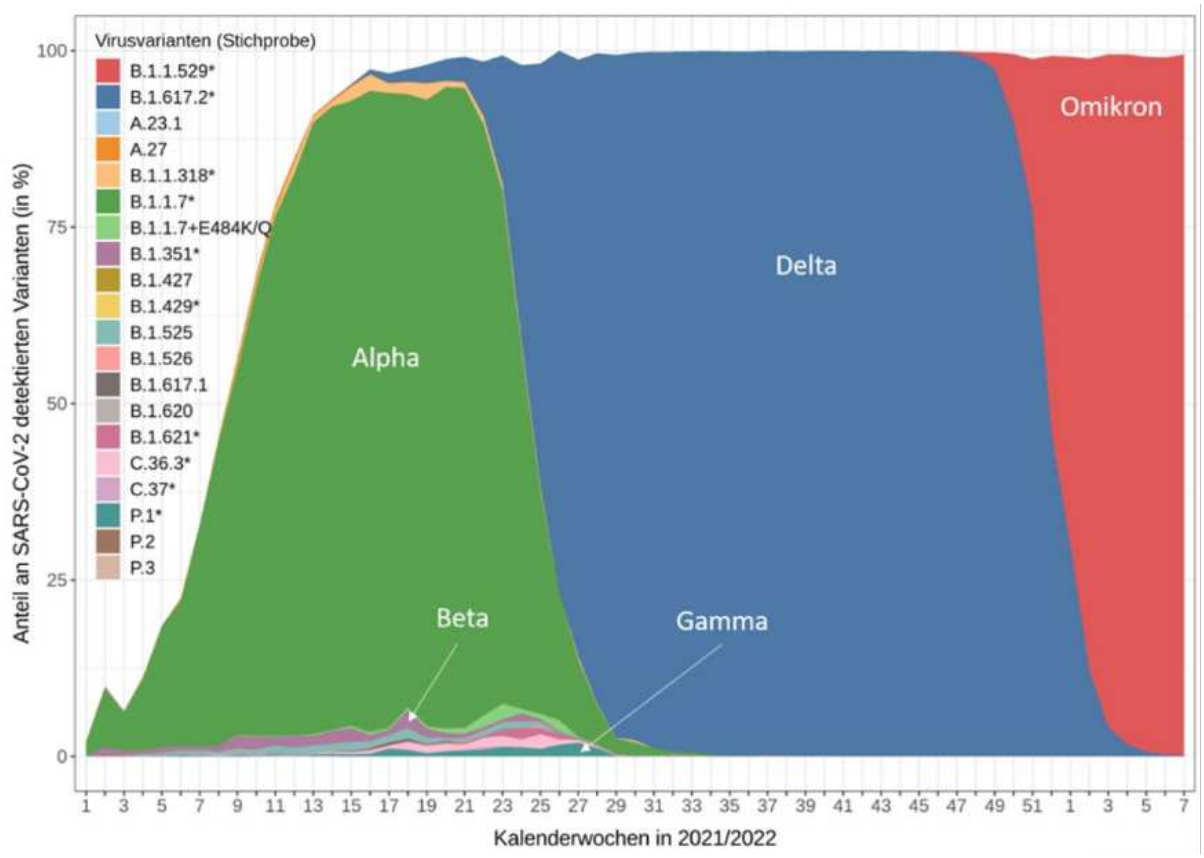
This variant was first discovered in India and was designated as a variant of concern by the WHO in May 2021. It exhibits clear evidence of increased transmissibility compared to the previously dominant Alpha (B.1.1.7) variant in Germany. Contact tracing data indicates that Delta (B.1.617.2) infections result in a higher proportion of infected contacts compared to Alpha (B.1.1.7) infections. Additionally, Delta variant infections have shown higher rates of hospitalization, intensive care admissions, and mortality, indicating increased virulence. The Delta (B.1.617.2) variant carries several mutations in its spike protein, including T19R, Deletion 157-158, L452R, T478K, D614G, P681R, and D950N. These mutations have also been associated with increased ACE2 receptor affinity, enhanced infectivity, and potential changes in antigenic properties. As with previous variants, laboratory experiments have demonstrated reduced neutralization of the Delta variant by convalescent sera. The Delta variant was detected in Germany since March 2021 and was the predominant variant for several months. Since the emergence of Omicron, samples of the Delta variant are rarely detected anymore (86,95,96).

1.3.5 Omicron (B.1.1.529 lineage)

The Omicron variant, also known as B.1.1.529, emerged in South Africa in November 2021 and quickly gained recognition as a VOC. It has over 30 mutations in the spike protein, and its emergence was associated with a significant increase in COVID-19 cases. Some of the reported mutations affect various parts of the virus, including the envelope, nucleocapsid

protein, matrix, spike protein, and receptor-binding domain. Omicron is highly infectious, with a 13-fold increase in viral infectivity compared to the Delta variant. Monoclonal antibodies that were previously authorized showed reduced effectiveness against Omicron. The variant quickly became dominant in many countries, giving rise to several subvariants (BA.1, BA.2, BA.3, BA.4, BA.5) (97,96,98).

Figure 2. Percentage shares of VOC and VOI based on the genomic sequences from the samples in Germany, 2021./2022. (99).



1.4 Olfactory dysfunction

The sense of smell, also known as olfaction, plays a crucial role in our daily lives, allowing us to perceive and interpret various scents and odors in our environment. Smelling is vital as it is linked to various emotions, but also serves as a warning system and helps to safeguard us against spoiled food or hazardous gases. Consequently, the loss of this crucial sense can lead to a dramatic reduction in quality of life. The process of smelling involves a complex interplay between the anatomy and physiology of our olfactory system.

1.4.1 Anatomy and physiology of the olfactory system

At the top of the nasal cavity, the olfactory epithelium contains olfactory receptor neurons (ORNs) with cilia that detect odorants. The nose's structure includes bony and cartilaginous elements, with the bony framework connected to the skull and cartilaginous plates supporting the outer nose. Within the nasal cavities, a septum separates them, covered by a mucous membrane composed of columnar ciliated epithelium and specialized olfactory membrane. Near the front of the lower septum, there is a small opening leading to a vestigial organ called Jacobson's organ. The septum's supporting framework consists of the ethmoid bone, vomer bone, and septal cartilage. The outer wall of each nasal cavity is divided into three meatuses by turbinated bones, with the superior meatus containing openings of the posterior ethmoidal air cells and the middle meatus featuring the bulla ethmoidalis. The middle meatus also has openings for the middle ethmoidal cells and a gutter called the hiatus semilunaris connecting to the frontal air sinus and the opening into the maxillary antrum.

Beneath the inferior turbinated bone lies the inferior meatus, revealing the valvular opening of the nasal duct. The roof of the nose serves as a passage for the olfactory nerves, while the wider floor creates a triangular shape (100).

The olfactory bulbs, located below the frontal lobes of the brain, receive axons from olfactory nerves and form spherical structures called olfactory glomeruli. Each glomerulus is connected to numerous olfactory receptor cells, allowing for the detection of faint odors through signal convergence. The axon bundles of mitral and tufted cells form the olfactory tracts, which project to the primary olfactory cortex in the temporal lobe and other regions of the brain, including the hypothalamus and amygdala. Unlike other sensory information, olfactory pathways bypass the thalamus and directly reach the cerebrum. To detect smells, inhaled in the nasal cavity allows odor molecules to reach the olfactory receptor cells. Odorant-binding proteins within the mucus interact with the receptors, stimulating olfactory receptor cells. This leads to the activation of G proteins and the generation of local potentials, which trigger action potentials and the release of neurotransmitters. The neurotransmitters bind to secondary neurons, propagating nerve signals through the olfactory pathways. This information reaches different brain regions, including the cerebral cortex for conscious perception, the hypothalamus for visceral reactions, and the amygdala for recognizing odors and associating them with emotions. Adaptation to smells occurs rapidly as the olfactory receptor cells adjust their sensitivity to prevent overstimulation (101).

1.4.2 Olfactory dysfunction as a symptom of COVID-19

Anosmia is a common chemosensory impairment in cases with COVID-19. It is considered one of the most significant and reliable indicators of SARS-CoV-2 infection. These impairments can manifest as decreased (hyposmia or hypogeusia) or complete loss of function (anosmia or ageusia). Other possible disturbances include distorted sensations (parosmia or parageusia), unpleasant odors or tastes (cacosmia or cacogeusia), and even hallucinations (phantosmia or phantogeusia) (102).

Research on the prevalence of chemosensory dysfunctions in COVID-19 initially presented varied results. A comprehensive review and meta-analysis by Butowt *et al.* involving 30.264 patients worldwide revealed that olfactory deficits were prevalent in approximately 44.1% of COVID-19 cases, while taste deficits were reported in around 43.3% of cases. The overall prevalence of any chemosensory deficits, encompassing both smell and taste, was estimated to be 49.0% (103). According to Mutiawati *et al.* the prevalence of anosmia in COVID-19 cases was estimated to be 38.2%, involving 107 studies and 32.142 patients. Similarly, the prevalence of dysgeusia was found to be 36.6% based on 101 studies and 30.901 patients (104).

It is important to note that these prevalence figures were derived from studies conducted in various regions, and there were observed differences between populations. Western countries demonstrated up to 3-times higher rates of chemosensory deficits compared to East Asia (103). The observed difference in anosmia prevalence between East Asians and Caucasians might be attributed to ethnic variations in the ACE2 protein. Caucasians tend to have a higher number of ACE2 variants expressed on their sustentacular cells, resulting in a stronger binding affinity for the SARS-CoV-2 virus and a higher frequency of olfactory symptoms. In comparison, East Asians have fewer ACE2 variants, leading to a lower incidence of anosmia (105).

The risk for olfactory dysfunction following an infection with the omicron variant, is significantly lower, ranging from 2 to 10 times less, compared to previous variants. This reduction applies to all ethnical groups (106).

1.4.3 Pathophysiology of anosmia in COVID-19

Mechanisms of anosmia in COVID-19 might be explained by four principal scenarios. The first scenario suggests that nasal obstruction, congestion, and rhinorrhea impede odorant access to the sensory epithelium, preventing them from binding to olfactory receptors. However, studies have ruled out this explanation since a significant number of COVID-19 patients with anosmia do not exhibit nasal congestion or rhinorrhea. Radiographic imaging also fails to show significant mucosal swelling (107,108).

The second scenario proposes that the virus directly infects and kills olfactory receptor neurons, resulting in sensorineural olfactory loss. Unfortunately, this explanation faces several inconsistencies. The time required for cellular regeneration and cilia maturation in olfactory receptor neurons is longer than the observed rapid recovery of smell in COVID-19 cases. Furthermore, mature olfactory neurons do not express significant levels of the viral entry proteins ACE2 and TMPRSS2 necessary for SARS-CoV-2 infection. Studies indicate that the virus primarily infects other cell types in the olfactory epithelium, such as sustentacular cells, rather than olfactory neurons (109,110).

The third scenario suggests that the virus infiltrates the brain, potentially from the nose, and affects the olfactory centers, leading to reduced smell sensations. However, the sudden loss of smell followed by rapid recovery observed in COVID-19 cases argues against this scenario. Olfactory receptor neurons, which provide a direct route for the virus to reach the brain, do not express the necessary entry proteins. Studies have not consistently shown acute accumulation of the virus in olfactory receptor neurons or the olfactory bulb within the initial stages of infection (111–113).

The fourth scenario proposes that the virus damages the support cells in the olfactory epithelium, particularly sustentacular cells, causing a transient impairment of smell. Sustentacular cells express the viral entry proteins ACE2 and TMPRSS2 and have been found to harbor the virus. Damage or inactivation of sustentacular cells can result in functional deficits in smell sensation. Notably, sustentacular cell regeneration occurs more rapidly than olfactory receptor neurons, explaining the observed rapid recovery of smell in most cases.

Taken together, current evidence suggests that damage to support cells in the olfactory epithelium, particularly sustentacular cells, may play a significant role in the transient loss of smell experienced by many COVID-19 patients. However, the specific functions of sustentacular cells in relation to smell sensation are still being investigated (114).

1.4.4 Anosmia as an early indicator of COVID-19

Based on the analyzed data from various studies, anosmia appears to be strongly associated with the occurrence of COVID-19. The prevalence of anosmia was found to be 10.2 times higher in patients with COVID-19 compared to those with COVID-19-like symptoms but negative RT-PCR for SARS-CoV-2. This suggests that anosmia can serve as an early indicator of COVID-19 (104). It has been suggested that anosmia may be a better predictor of COVID-19 than other well-known symptoms such as fever and cough (115). However, for a definitive diagnosis, it is advised to consult healthcare professionals who can provide proper molecular testing and confirmation, using a NAAT.

1.4.5 Long-term implications of anosmia in COVID-19

According to a meta-analysis by Kye Jyn Tan et al., the recovery of smell and taste after COVID-19 infection follows a positive trend. At 30 days, approximately 74% of patients reported smell recovery, and 79% reported taste recovery. These percentages increased to 86% and 88% at 60 days, 90% and 90% at 90 days, and 96% and 98% at 180 days for smell and taste recovery, respectively. However, the analysis estimated that around 5% of patients may experience persistent smell or taste dysfunction after COVID-19. Female sex was found to be associated with poorer recovery of smell and taste, although the exact reasons for this association are not fully understood. Possible factors contributing to this difference could include baseline olfaction and gustation, hormonal factors, or genetic variations. Interestingly, the analysis also noted faster taste recovery in Asian countries compared to other continents. (116).

A study, conducted in Argentina, followed 766 older adults over the course of one year and found that those who experienced anosmia were more likely to have cognitive impairments, particularly in memory and attention. The severity of anosmia, rather than the severity of COVID-19, was a significant predictor of cognitive impairment (117).

Wingrove *et al.* found, that individuals with anosmia exhibit specific brain connectivity patterns. They show increased connectivity between the left orbitofrontal cortex, visual association cortex, and cerebellum, while experiencing reduced connectivity between the right orbitofrontal cortex and dorsal anterior cingulate cortex. Moreover, those with anosmia demonstrate higher cerebral blood flow in the left insula, hippocampus, and ventral posterior cingulate compared to individuals who have resolved their anosmia (118). These findings provide insights into the neural correlates of anosmia and may contribute to a better understanding of the condition.

Patients experiencing anosmia as postacute sequelae of SARS-CoV-2 infection (PASC) show distinct immunological responses compared to those with acute COVID-19. PASC patients with anosmia exhibited infiltrates of T cells, interferon response signatures, and specific lymphocyte populations in the olfactory epithelium samples. Although the mechanisms behind sensory dysfunction in PASC remain unclear, macrophage analysis in severe COVID-19 patients indicates a proinflammatory reprogramming during acute infections, leading to long-term changes in other immune cell functions (119).

The long-term implications of anosmia in COVID-19 encompass various aspects. Understanding these implications is crucial for comprehensive management and care of individuals affected by anosmia.

2. OBJECTIVES

2.1 Aims of the study

The prolonged health effects experienced by individuals after recovering from COVID-19, has emerged as a significant concern. To enhance our understanding of post-COVID complications, this cross-sectional survey study aims to collect new and additional data on symptom prevalence, severity, and duration, while also comparing different virus variants of concern. A comprehensive questionnaire collected demographic and clinical data, enabling to explore potential associations between modifiable and non-modifiable risk factors and the prevalence or severity of symptoms after COVID-19 infection. In the following there will be pronounced emphasis on olfactory dysfunction and its potential correlation with influencing parameters and concurrent symptoms.

The primary objectives of this study are as follows:

1. To assess the prevalence, severity, and duration of symptoms associated with Long-Covid among hospitalized individuals who have recovered from COVID-19.
2. To compare the symptom profiles of different virus variants in Long-Covid patients, exploring potential variations in symptom presentation, severity, and duration.
3. To examine the occurrence and characteristics of anosmia as a symptom of Long-Covid, including its prevalence, intensity, and duration.
4. To identify potential influencing parameters associated with the occurrence and severity of anosmia in Long-Covid patients. These parameters may include demographic factors, status of vaccination, smoking or alcohol consumption.
5. To investigate potential correlations between anosmia and other concurrent symptoms commonly reported in Long-Covid patients, such as gustatory dysfunction, headache, fatigue, cognitive impairment or changes in body weight.
6. To examine the demographics of immunity, including the vaccination status and gender distribution among participants and across phases of COVID-19.
7. To examine the response rate of survey participants and compare the demographics of respondents and non-respondents.

2.2 Hypothesis

Postacute Anosmia differs according to the relevant SARS-CoV-2 strains.

3. MATERIALS AND METHODS

3.1 Study design

This cross-sectional survey study aimed to assess the long COVID symptoms experienced by former hospitalized patients at the Coburg REGIOMED hospital. The study population was divided into four phases based on the COVID-19 virus variant that was prevalent in accordance with the epidemiological data from the Robert Koch Institute. The study employed a voluntary and anonymous survey participation approach. Participants were provided with detailed information about the study objectives and procedures, and they were asked to provide informed consent at the beginning of the questionnaire. No monetary compensation was offered to the participants. By ensuring anonymity and voluntary participation, the study aimed to minimize any potential bias and encourage honest responses from the participants. The survey instrument consisted of a structured questionnaire developed based on existing literature and validated measures related to long COVID symptoms. Data collection was conducted through an online platform (LamaPoll), allowing participants to complete the survey remotely and at their convenience. The survey remained accessible from September 2022. until December 2022. to ensure an adequate sample size and representation of the selected study population.

3.2 Data collection

Data for this study was obtained through a combination of clinical records from the ORBIS hospital documentation system and responses from the online questionnaire. The target population consisted of 1430 former patients who were hospitalized with the ICD code for SARS-CoV-2 (U07.1) as either their primary or secondary diagnosis between March 16th 2020., and March 30th 2022.

To achieve pseudo-anonymized data collection, each participant was assigned an individual case number, allowing only the researcher team to evaluate the data. Out of the target population, 1025 participants received a cover letter with an invitation, introduction, detailed instructions, and a QR code to access the questionnaire. LamaPoll is an online survey tool that provides various features for creating and conducting surveys. It emphasizes data privacy and security, complying with GDPR regulations, and holding ISO 27001 certification. Additionally, to increase the response rate among older participants who might not have digital access to the questionnaire, a prepaid return envelope with the same questionnaire in printed form was included in the letter. This allowed participants to easily complete the survey and return it via mail without needing digital means.

405 individuals from the initial study population were excluded from the study as they were either deceased or discharged into a nursing home. Additionally, responses from pediatric patients and other exclusion criteria were sorted out. Overall response rate from the survey was 14,3% (n=147).

The combined dataset used for the final analysis included the 147 survey responses supplemented with data from the corresponding clinical records. The matching of both data sets was done based on the respective case numbers. By including the case number on both the digital and printed versions of the questionnaire, it was possible to link the responses and ensure accurate data analysis.

3.3 Variables

The variables considered in this study can be divided into modifiable and non-modifiable risk factors. Included modifiable risk factors were education, nutrition, smoking history in pack-years, and alcohol consumption per day and week. Participants were also asked about their pre- and post-infection lifestyle, such as exercise activity level, changes in general health status, concentration abilities, psychological status, changes in body weight, and presence or absence of pain.

Immunization status was another modifiable risk factor investigated, categorized as unvaccinated, one dose, two doses, booster dose or natural immunity after recovery from COVID-19 infection. It is important to mention that no specific differentiation was made based on the manufacturer and type of vaccine. The survey also gathered information on participants' comorbidities and pharmacotherapy.

In addition to modifiable risk factors, the survey primarily emphasized the presence and duration of postacute COVID-19 syndrome. The duration of symptoms was categorized based on the NICE classification: Acute COVID-19 refers to signs and symptoms lasting up to 4 weeks. Ongoing symptomatic COVID-19 occurs from 4 to 12 weeks. Post COVID-19 syndrome refers to signs and symptoms lasting more than 12 weeks without another explanation. By definition "long COVID" encompasses both ongoing symptomatic (4-12 weeks) and post COVID-19 syndrome (>12 weeks) (120).

On the other hand, non-modifiable risk factors encompassed variables collected through the Orbis system. These included the date of first positive PCR test result, the presence of COVID-related symptoms on admission, body weight, height, and BMI. For individuals admitted to the intensive care unit (ICU), data on the duration of ICU stay and .the type of ventilatory support were recorded.

3.3.1 COVID-19 phases in Germany

The assignment of participants to the wild-type or a particular virus variant of concern was made, based on epidemiological data from RKI, categorized into most prevalent VOCs and calendar weeks (121):

Phase 1: Wild-type variant, 10/2020 to 8/2021.

Phase 2: Alpha variant, 9/2021. to 30/2021.

Phase 3: Delta variant, 31/2021. to 51/2021.

Phase 4: Omicron variant, 52/2021. to March 2022.

3.4 Ethical approval

The research project described in this paper was subjected to ethical review according to the regulations outlined in §2 of the statutes for the Institutional Review Board (IRB) of the Medical School REGIOMED Coburg. The IRB committee carefully evaluated the project and found no objections to the implementation of the research project. The study was carried out in accordance with the principles stated in the Declaration of Helsinki. Confidentiality was strictly maintained, and all data collected were securely stored and accessible only to the research team.

3.5 Statistical analysis

The data collected from the questionnaire in this cross-sectional survey study was subjected to rigorous statistical analysis. Descriptive statistics were employed to summarize the demographic characteristics of the study participants, including mean, standard deviation, median, and frequency distributions. This allowed for a comprehensive understanding of the sample population. To assess the association between different variables, commonly used statistical tests were utilized. For investigating the relationship between long COVID symptoms and categorical variables (such as gender or age groups), the Chi-square and Fisher exact test were employed. When examining continuous variables, non-parametric alternatives like the Mann-Whitney U test were employed as no normal distribution could be assumed. Furthermore, Logistic regressions were performed to explore the relationship between variables.. All statistical analyses were performed using appropriate software (STATA16, Stata Corp, College Station TC, USA), and a significance level (alpha) of 0.05 was used to determine statistical significance.

4. Results

4.1 Demographic description of the study population

4.1.1 Demographics of hospitalized patient sample

The study population consisted of 1430 participants, of which gender information was available for analysis. Among the participants, 731 (51.1%) were identified as male, while 699 (48.9%) were identified as female. This distribution indicates a relatively balanced representation of both genders in the study.

To gain further insights into the population, an age analysis was conducted. For male participants: Age 18 to 101, mean 69.94 +/- 15.95. Median 73 years.
For female participants: Age 18 to 100, mean 70.24 +/- 19.73. Median 76 years.
For the entire population: Age 18 to 101, mean 70.09 +/- 17.89. Median 74 years.

A rank-sum (Mann-Whitney) test was conducted to assess any significant differences in age between genders. The test revealed a non-significant result ($z = -2.554$, $p > 0.05$), suggesting that there were no significant differences in age between males and females in the study population.

Additionally, the study population was categorized into four phases, and an age analysis was conducted within each phase. The mean ages for each phase were as follows: Phase 1 (mean = 74.86 years, SD = 15.66), Phase 2 (mean = 62.58 years, SD = 18.30), Phase 3 (mean = 69.81 years, SD = 15.87), and Phase 4 (mean = 66.20 years, SD = 20.50). A Kruskal-Wallis test indicated a statistically significant difference in age among the four phases (chi-squared = 93.326, $p < 0.001$).

The study population consisted of a relatively balanced representation of males and females. The age distribution showed a comparable mean age for both genders, with no significant difference detected. However, significant variations in age were observed across different phases of the study.

4.1.2 Demographics of survey sample

From the initial study population involving 1430 participants, 405 were classified as unsuitable for follow-up **(Figure 2)**. 56 did not meet inclusion criteria, 76 required nursing facility care, 3 underwent respiratory rehabilitation, and sadly, 270 participants had passed away. Finally, the survey study included a sample of 1025 individuals. Out of these, 147 participated in the survey **(Table 2)**, while 878 did not respond.

Figure 2. Consort diagram of study population

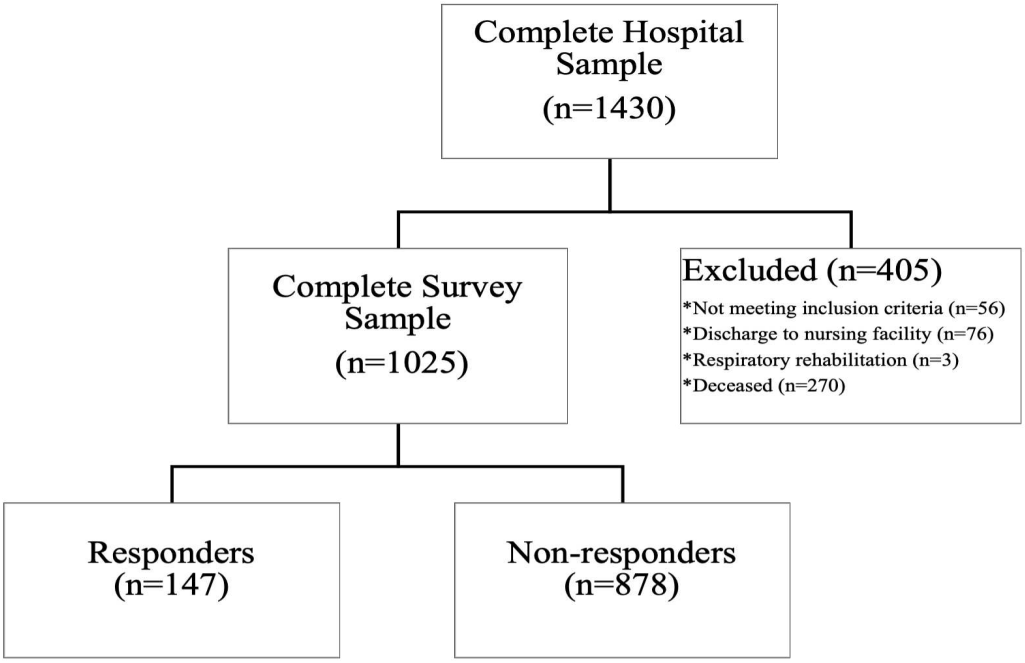


Table 2. Response rate of survey participants across phases

	Total Sample	***Phase 1***	***Phase 2***	***Phase 3***	***Phase 4***
Total Sample	1025	406	156	204	259
	100%	100%	100%	100%	100%
No Response	878	343	125	179	231
	85.7%	84.5%	80.1%	87.8%	89.2%
Response	147	63	31	25	28
	14.3%	15.52%	19.%	12.3%	10.8%

4.1.3 Age and gender distribution across phases

Table 3. Age distribution across phases

	Responder	***Non-responder***	***Phase 1***	***Phase 2***	***Phase 3***	***Phase 4***
Mean Age	65.13	67.39	66.46	60.87	65.2	66.79
Median Age	65	72	65	62	68	71
Standard Deviation	15.40	19.17	13.52	15.37	17.25	17.56
Minimum Age	21	18	34	23	27	21
Maximum Age	94	101	94	83	87	86

Table 4. Gender distribution across 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%

Table 3 and 4 provide a comprehensive representation of the age and gender distribution among the study participants of different phases.

The non-significant chi-square test result ($p = 0.516$) supports the lack of a significant relationship between gender and phase.

The respondents' mean age was 65.13 years (SD = 15.40, range 21-94, median 65), while the non-respondents had a mean age of 67.39 years (SD = 19.17, range 18-101, median 72). A Mann-Whitney U test showed a significant difference in rank sums between the two groups ($z = 2.620$, $p = 0.0088$), indicating a statistically significant age difference.

In conclusion, respondents were generally slightly younger, with a narrower age range compared to non-respondents. These findings suggest that age may influence survey participation and should be considered when interpreting the results

4.2 Status of immunity

In addition to the collected demographic data such as gender and age, participants were also surveyed about their immune status. It's worth noting that individuals who had naturally acquired immunity after recovery from COVID-19 infection, were considered equivalent to having received one dose of vaccination. 144 participants provided information about their status of vaccination. Subsequently, they were categorized into unvaccinated or vaccinated, depending on the number of administered doses. The group of non-immunized comprised 94 participants (65.3%), while 11 individuals (7.6%) had received one dose, 21 individuals (14.6%) had received two doses, and the remaining 18 participants (12.5%) had received three doses or immunization events (vaccination or infections), respectively.

Additionally, the sample was divided into males and females. Out of the 78 male participants, 45 (57.7%) were unvaccinated, 10 (12.8%) had received one vaccination, 13 (16.7%) had received two vaccinations, and 10 (12.8%) had received three vaccinations. Among the 66 female participants, 49 (74.2%) had not been immunized, while 1 individual (1.5%) had received one vaccination, 8 individuals (12.1%) had received two vaccinations, and the remaining 8 individuals (12.1%) had received three vaccinations. In conclusion, a larger proportion of males were vaccinated compared to females. Furthermore, the data has revealed that the majority of responses (66%) were attributed to participants without an immune status.

Table 5. Status of immunity according to gender

	Male Gender	***Female Gender***	***Total Sample***
Non-Immunized	57.7% (n=45)	74.2% (n=49)	65.3% (n=94)
One Immunization	12.8% (n=10)	1.5% (n=1)	7.6% (n=11)
Two Immunizations	16.7% (n=13)	12.12 (n=8)	14.6% (n=21)
Three Immunizations	12.8% (n=10)	12.1% (n=8)	12.5% (n=18)
Total Sample	100% (n=78)	100% (n=66)	100% (n=144)

In Conclusion, the respondents were generally younger than the non-respondents, suggesting age may affect survey participation. Overall, the survey participants exhibited a relatively balanced representation of genders, with comparable mean ages for males and females. The age distribution varied across different phases, and a larger proportion of males were vaccinated compared to females. Additionally, a significant majority of the responses were from participants without an immune status.

4.3 Anosmia

4.3.1 Olfactory dysfunction and gender

The analysis of our survey data uncovered intriguing findings regarding the correlation between gender and the sense of smell **(Table 6)**. Out of the total 147 individuals, there were 80 males and 67 females. When examining the levels of anosmia, it was observed that 54 males (67.5%) and 38 females (56.7%) reported no olfactory dysfunction. Conversely, 17 males (21.3%) and 16 females (23.9%) experienced hyposmia, while 9 males (11.3%) and 13 females (19.4%) reported anosmia.

To determine the statistical significance of these observed differences, a Pearson chi-square test was conducted. The resulting chi-square value was 2.409, accompanied by a corresponding p-value of 0.300. The non-significant p-value indicates a lack of substantial evidence supporting an association between gender and the sense of smell based on our survey data.

4.3.2 Duration of olfactory dysfunction and gender

The duration of olfactory dysfunction presented as follows **(Table 6)**.

Among the males, 11.3% (n=9) reported olfactory dysfunction for 1-4 weeks, 5.0% (n=4) had it for 4-12 weeks, and 16.3% (n=13) had a duration longer than 12 weeks. Among the females, 13.4% (n=9) reported olfactory dysfunction for 1-4 weeks, 11.9% (n=8) had it for 4-12 weeks, and 17.9% (n=12) had a duration longer than 12 weeks.

Analyzing the data using a chi-squared test, with a test statistic of 3.030 and a p-value of 0.387, we find that the relationship between gender and the duration of olfactory dysfunction is not statistically significant.

Table 6. Olfactory dysfunction and duration sorted by gender

	Male Gender	***Female Gender***	***Total Sample***
No olfactory dysfunction	67.5% (n=54)	56.7% (n=38)	92
Hyposmia	21.3% (n=17)	23.9% (n=16)	33
Anosmia	11.3% (n=9)	19.4% (n=13)	22
Duration < 4 weeks	11.3% (n=9)	13.% (n=9)	18
Duration 4 - 12 weeks	5.0% (n=4)	11.9% (n=8)	12
Duration >12 weeks	16.3% (n=13)	17.% (n=12)	25
Duration total	32.5% (n=26)	43.3% (n=29)	55
Total sample	100% (n=80)	100% (n=67)	147

4.3.3 Olfactory dysfunction and age

Table 7. Olfactory dysfunction and age

	Mean	***SD***	***p50***	***Min***	***Max***
No olfactory dysfunction	67.13	14.23	67.5	21	94
Olfactory dysfunction	61.78	16.79	62	23	92
Total	65.13	15.40	65	21	94

A two-sample Wilcoxon rank-sum test was conducted to compare the age distributions between participants with and without olfactory dysfunction. The test yielded a test statistic (z-value) of 1.720, with a corresponding p-value of 0.0854. This p-value suggests that there may be a chance to reject the null hypothesis if the sample size was larger.

In summary, based on the data provided, there is a trend indicating that individuals without olfactory dysfunction tend to be older on average compared to those with olfactory dysfunction. However, further investigation or a larger sample size may be required to establish a statistically significant relationship between olfactory dysfunction and age.

4.3.4 Olfactory dysfunction and phases

The analysis of frequency distribution revealed varying numbers of individuals in different phases based on their olfactory dysfunction level **(Table 8)**. Among participants with no olfactory dysfunction, phase 1 – 4 had 33/18/17/24 individuals, respectively. The column percentages were calculated to determine the proportion of individuals with no dysfunction within each phase, ranging from 52.% in phase 1 to 85.7% in phase 4.

Interestingly, when considering the total number of participants with olfactory dysfunctions, regardless of symptom severity, a statistically significant correlation (p=0.021) between olfactory dysfunction and phase becomes evident. These findings suggest that there may be a trend where the likelihood of experiencing olfactory dysfunction decreases as the phases progress from 1 to 4.

4.3.5 Duration of olfactory dysfunction and phases

Table 8 also includes the distribution of the duration of olfactory dysfunction categorized based on the duration in weeks. It also provides the frequency and column percentages for each phase of COVID-19.

The Pearson chi-square test statistic is 14.571 with a corresponding p-value of 0.103, indicating that there is no statistically significant association between the duration of olfactory dysfunction and the phase of COVID-19.

Table 8. Olfactory dysfunction and duration across phases

	Phase 1	***Phase 2***	***Phase 3***	***Phase 4***	***Total sample***
No olfactory dysfunction	52.4% (n=33)	58.% (n=18)	68.00% (n=17)	85.7% (n=24)	92
Dysfunction (total)	47.6% (n=30)	41.9% (n=13)	32.0% (n=8)	14.3% (n=4)	55
Hyposmia	(n=17)	(n=7)	(n=6)	(n=3)	33
Anosmia	(n=13)	(n=6)	(n=2)	(n=1)	22
Duration < 4 weeks	12.7% (n=8)	16.% (n=5)	8.0% (n=2)	10.7% (n=3)	18
Duration 4 - 12 weeks	7.9% (n=5)	9.7% (n=3)	12.0% (n=3)	3.6% (n=1)	12
Duration >12 weeks	27.0% (n=17)	16.1% (n=5)	12.0% (n=3)	0% (n=0)	25
Duration (total)	100% (n=63)	100% (n=31)	100% (n=25)	100% (n=28)	55
Total sample	63	31	25	28	147

4.3.6 Correlation of olfactory dysfunction with age, phase, and gender

Table 9. Ordered logistic regression of olfactory dysfunction and age, phase, gender

	Coefficient	***Std. Err.***	***Z***	***P>|z|***	***[95% Conf. Interval]***	
Age	-.0319161	.0133972	-2.38	0.017	-.0581741	-.0056581
Phase	-.4027383	.1879081	-2.14	0.032	-.7710313	-.0344453
Gender	.7956365	.390741	2.04	0.042	.0297981	1.561475

The ordered logistic regression model **(Table 9)** shows that olfactory dysfunction is influenced by three predictors: age, gender, and phase. The analysis suggests the following relationships:

1. Increasing age is associated with a decrease in the likelihood of being in a higher category of olfactory dysfunction (coefficient: -0.032). In other words, as age increases, the probability of having a higher level of olfactory dysfunction decreases.

2. As phase increases, the probability of being in a higher category of olfactory dysfunction decreases (coefficient: -0.403). This implies that the phase has a negative effect on the outcome of olfactory dysfunction.

3. The coefficient for gender is positive (0.796), indicating that being female (coded as 1) is associated with a higher likelihood of being in a higher category of olfactory dysfunction compared to males (coded as 0).

The overall model chi-square test suggests that the predictors collectively have a significant effect on olfactory dysfunction. The pseudo-R-squared value indicates that approximately 7.5% of the variance in olfactory dysfunction can be explained by the predictors. LR chi-square test has a p-value of 0.0011, suggesting that the overall model is statistically significant.

4.3.7 Olfactory dysfunction and status of vaccination

Based on our study, it appears that a larger proportion of both vaccinated (76.2%) and unvaccinated (57.1%) individuals did not experience olfactory dysfunction **(Table 10)**. However, among the vaccinated group, including those with natural immunity, the percentage of individuals reporting no olfactory dysfunction was higher. The specific types of olfactory dysfunction were also less prevalent among the vaccinated group compared to the unvaccinated group.

To explore the relationship between vaccination status and olfactory dysfunction, a Pearson chi-square test was conducted. Although the p-value of 0.081 did not reach conventional statistical significance ($p < 0.05$), it suggests a potential association between vaccination status and olfactory dysfunction. Further investigation with larger sample sizes would be warranted to better understand this potential association.

4.3.8 Olfactory dysfunction and degree of immunization

A total of 144 individuals were included in this test. Participants' vaccination status was categorized into four groups: unvaccinated, individuals that received one dose or had natural immunity, individuals with two doses, and individuals with three doses. The sense of smell was again assessed using a three-category scale: no olfactory dysfunction, hyposmia, and anosmia.

The distribution of participants across different combinations of vaccination status and olfactory dysfunction categories is presented in **Table 10**. Among those who received one dose or had natural immunity, only one person reported hyposmia and only one person reported anosmia. This corresponds to a column percentage of 9.1%, each. In a similar manner, individuals who received two doses displayed hyposmia at a rate of 19.1% (n=4) and anosmia at a rate of 14.3% (n=3). Likewise, among those who received three doses, hyposmia was observed in 16.7% of cases (n=3), while no case of anosmia was reported (n=0).

To gain a comprehensive understanding, we examine the row percentages. They allow us to analyze the distribution of olfactory dysfunction within each vaccination group. The table suggests that there may not be a statistically significant association between the number of vaccine doses and the occurrence of olfactory dysfunction. This is indicated by the Pearson chi-squared value of 8.888 and a corresponding probability of 0.180. However, further analysis and consideration of sample size, type of vaccine and time between immunization and infection might yield more conclusive results.

Table 10. Olfactory dysfunction and status of immunity

Vaccination Status	*No olfactory dysfunction*	*Hyposmia*	*Anosmia*	*Total*
Unvaccinated	57.1%	24.8%	18.1%	100% (n=105)
Vaccinated (Total)	76.2%	16.7%	7.1%	100% (n=42)
One doses/ Natural immunity	81.8%	9.1%	9.1%	100% (n=11)
Two doses	66.7%	19.1%	14.3%	100% (n=21)
Three doses	83.3%	16.7%	0%	100% (n=18)

4.3.9 Olfactory dysfunction and smoking

Table 11. Olfactory dysfunction and smoking

	Nonsmoker	*Smoker*	*Total sample*
No olfactory dysfunction	66.3% (n=61)	33.7% (n=31)	100% (n=92)
Olfactory dysfunction	65.5% (n=36)	34.6% (n=19)	100% (n=55)
Duration < 4 weeks	12	6	18
Duration 4 - 12 weeks	7	5	12
Duration >12 weeks	17	8	25
Total sample	97	50	147

The results of the chi-square tests indicate that there is no significant association between smoking status and olfactory dysfunction, as well as between the duration of olfactory dysfunction and smoking status **(Table 11)**. In both cases, the Pearson chi-square values (0.011 and 0.366) and the corresponding p-values (0.916 and 0.947) suggest that any observed relationship between these factors is likely due to chance rather than a meaningful connection. Although a more detailed analysis of smoking behavior and pack-years of smoking was collected, it was not considered in this evaluation. The group of individuals who used to smoke was classified as part of the nonsmoker group.

4.3.10 Olfactory dysfunction and alcohol

Table 12. Olfactory dysfunction and alcohol

	No alcohol	***Alcohol***	***Total sample***
No olfactory dysfunction	47.8% (n=44)	52.2% (n=48)	100% (n=92)
Olfactory dysfunction	40.0% (n=22)	60.0% (n=33)	100% (n=55)
Duration < 4 weeks	6	12	18
Duration 4 - 12 weeks	7	5	12
Duration >12 weeks	9	16	25
Total sample	66	81	147

For olfactory dysfunction and alcohol consumption, the chi-square test yields a Pearson chi-square value of 0.852 with a p-value of 0.356. Since the p-value is greater than 0.05, there is no significant association between olfactory dysfunction and alcohol consumption.

Similarly, for the duration of olfactory dysfunction and alcohol, the chi-square test results in a Pearson chi-square value of 2.968 with a p-value of 0.397. Again, the p-value is greater than 0.05, indicating that there is no significant association between the duration of olfactory dysfunction and alcohol consumption.

The significance of these parameters is limited since this analysis ignored the quantity of alcohol consumption. Consuming one beer per week was considered equivalent to consuming large amounts on a daily basis.

4.3.11 Olfactory and gustatory dysfunction

Table 13. Olfactory and gustatory dysfunction across phases

	Phase 1	***Phase 2***	***Phase 3***	***Phase 4***	***Total***
No olfactory dysfunction	33 (35.9%)	18 (19.6%)	17 (18.5%)	24 (26.1%)	92 (100%)
Hyposmia	17 (51.5%)	7 (21.2%)	6 (18.2%)	3 (9.1%)	33 (100%)
Anosmia	13 (59.1%)	6 (27.3%)	2 (9.1%)	1 (4.5%)	22 (100%)
No gustatory dysfunction	22 (30.1%)	17 (23.3%)	15 (20.5%)	19 (26.0%)	73 (100%)
Hypogeusia	24 (51.1%)	8 (17.0%)	8 (17.0%)	7 (14.9%)	47 (100%)
Ageusia	17 (63.0%)	6 (22.2%)	2 (7.4%)	2 (7.4%)	27 (100%)
Isol. hyposmia	1 (50.0%)	1 (50.0%)	0	0	2 (100%)
Isol. anosmia	0	1 (100%)	0	0	1 (100%)
Isol. hypogeusia	7 (41.2%)	3 (17.6%)	2 (11.8%)	5 (29.4%)	17 (100%)
Isol. ageusia	5 (100%)	0	0	0	5 (100%)
No olfactory or gustatory dysfunction	21 (30.0%)	15 (21.4%)	15 (21.4%)	19 (27.1%)	70 (100%)
Both olfactory and gustatory dysfunction	29 (55.8%)	11 (21.2%)	8 (15.4%)	4 (7.7%)	52 (100%)
Pearson Chi2	43.603	30.401	41.544	22.333	125.0852
p-Value	0.000	0.000	0.000	0.000	0.000
Total Sample	63 (42.9%)	31 (21.1%)	25 (17.0%)	28 (19.0%)	147 (100%)

There appears to be a strong association between olfactory and gustatory dysfunction based on the chi-square test results provided. The p-value for the overall association is less than 0.0001. Additionally, the chi-square tests conducted for each phase also yielded the same significant p-values (all < 0.0001), suggesting that the association between smell and taste is present in each phase analyzed.

4.3.12 Olfactory dysfunction and memory difficulties

Table 14. Olfactory dysfunction and memory difficulties across phases

	Phase 1	***Phase 2***	***Phase 3***	***Phase 4***	***Total***
No olfactory dysfunction	33 (35.9%)	18 (19.6%)	17 (18.5%)	24 (26.1%)	92 (100%)
Hyposmia	17 (51.5%)	7 (21.2%)	6 (18.2%)	3 (9.1%)	33 (100%)
Anosmia	13 (59.1%)	6 (27.3%)	2 (9.1%)	1 (4.5%)	22 (100%)
No memory difficulty	31 (37.3%)	15 (18.1%)	14 (16.9%)	23 (27.7%)	83 (100%)
Memory difficulty	32 (50.0%)	16 (25.0%)	11 (17.2%)	5 (7.8%)	64 (100%)
Isolated hyposmia or anosmia	12 (50.0%)	5 (20.8%)	5 (20.8%)	2 (8.3%)	24 (100%)
Isolated memory difficulty	14 (42.4%)	8 (24.2%)	8 (24.2%)	3 (9.1%)	33 (100%)
No olfactory or memory difficulty	19 (32.2%)	10 (16.9%)	9 (15.3%)	21 (35.6%)	59 (100%)
Both olfactory and memory difficulty	18 (58.1%)	8 (25.8%)	3 (9.7%)	2 (6.5%)	31 (100%)
Pearson Chi2	2.2898	1.0005	1.7236	5.5594	5.9305
p-Value	0.318	0.608	0.422	0.062	0.052
Total Sample	63 (42.9%)	31 (21.1%)	25 (17.0%)	28 (19.0%)	147 (100%)

The analysis found a barely detectable statistical significance (p=0.052) between olfactory dysfunction and memory difficulty. When examining each phase separately, no consistent relationship was observed between these variables.

4.3.13 Olfactory dysfunction and headache

Table 15. Olfactory dysfunction and headache

	No headache	***Headache***	***Total sample***
No olfactory dysfunction	84.8% (n=78)	15.2% (n=14)	100% (n=92)
Olfactory dysfunction	61.8% (n=34)	38.% (n=21)	100% (n=55)
Total sample	112	35	147

After conducting a Fisher's exact test, the obtained p-value was 0.002, which suggests a strong and statistically significant association between headache and olfactory dysfunction.

4.3.14 Olfactory dysfunction and tiredness

Table 16. Olfactory dysfunction and tiredness

	No tiredness	***Tiredness***	***Total sample***
No olfactory dysfunction	43.3% (n=39)	56.7% (n=51)	100% (n=90)
Olfactory dysfunction	16.4% (n=9)	83.6% (n=46)	100% (n=55)
Total sample	48	97	145

The analysis conducted using a chi-square test indicates that there is a significant association (Pearson chi square(1) = 11.213, Pr = 0.001) between olfactory dysfunction and tiredness in the provided data.

4.3.15 Olfactory dysfunction and fatigue

Table 17. Olfactory dysfunction and fatigue

	No fatigue	***Fatigue***	***Total sample***
No olfactory dysfunction	45.7% (n=42)	54.4% (n=50)	100% (n=92)
Olfactory dysfunction	7.3% (n=4)	92.7% (n=51)	100% (n=55)
Total sample	46	101	147

The chi-square test conducted on this data yields a Pearson chi-square value of 23.582 and a p-value of 0.000. This indicates a significant association between olfactory dysfunction and fatigue.

4.3.16 Olfactory dysfunction and concentration difficulties

Table 18. Olfactory dysfunction and concentration difficulties

	No concentration difficulty	***Concentration difficulty***	***Total sample***
No olfactory dysfunction	67.4% (n=62)	32.6% (n=30)	100% (n=92)
Olfactory dysfunction	42.6% (n=23)	57.4% (n=31)	100% (n=54)
Total sample	85	61	146

The chi-square test statistic is 8.603, and the associated p-value is 0.003. This indicates a significant association between olfactory dysfunction and concentration difficulties.

4.3.17 Olfactory dysfunction and weight loss

Table 19. Olfactory dysfunction and weight loss (in kg)

Geruch	*n*	*mean*	*sd*	*min*	*max*	*p50*	*Rank Sum*	*Chi2*	*p-Value*
0	16	-11.5	7.1	-25	-4	-9	287.5		
1	14	-10.5	7.3	-25	-4	-7.5	277.5	0.256	0.880
2	7	-9.9	6.0	-20	-3	-10	138.0	0.259	0.879
Total	37	-10.8	6.8	-25	-3	-9			

Kruskal-Wallis equality of populations rank test

Chi-Squared test

For individuals with no olfactory dysfunction, there were 16 observations. On average, they experienced a weight loss of -11.5 kg, with a standard deviation of 7.06 kg. The range of weight loss varied from -25 kg to -4 kg, with a median weight loss of -9 kg.

In the case of individuals with hyposmia, there were 14 observations. On average, they had a weight loss of -10.5 kg, with a standard deviation of 7.28 kg. The range of weight loss ranged from -25 kg to -3 kg, with a median weight loss of -7.5 kg.

For individuals with anosmia, there were 7 observations. On average, they experienced a weight loss of -9.86 kg, with a standard deviation of 5.98 kg. The range of weight loss varied from -20 kg to -3 kg, with a median weight loss of -10 kg.

The Kruskal-Wallis test was conducted to determine if there were significant differences in weight loss across varying degrees of olfactory dysfunction. The results of the test suggest that there is no significant difference (chi-squared = 0.256, p = 0.880). Even though no association between olfactory dysfunction and weight loss could be found in these data, the mean weight loss of 10.81 kg is still noteworthy.

5. DISCUSSION

The discussion section of this diploma thesis centers around analyzing and interpreting the gathered data concerning post-COVID-19 symptoms, particularly olfactory dysfunction. It also explores potential correlations between these symptoms and other factors, along with accompanying symptoms. Additionally, a concise comparison shall be provided, contrasting these findings with the current state of the literature. Unfortunately, there are only a few studies available that provide insight into the specific features and associations of anosmia as an individual symptom. Instead, many studies focus on examining post-acute COVID-19 syndrome as a comprehensive condition.

When examining the correlation between gender and the sense of smell, our data does not provide substantial evidence supporting an association between gender and olfactory dysfunction. The prevalence of anosmia and hyposmia was similar between males and females. However, there appears to be a trend suggesting that individuals without olfactory dysfunction tend to be older on average compared to those with olfactory dysfunction. This trend indicates that age may play a role in the presence and severity of olfactory dysfunction.

The findings from the ordered logistic regression analysis reveal distinct risk patterns for the development of olfactory dysfunction. According to the analysis, individuals at a younger age, female gender, and those who experienced infection during an earlier timepoint of the pandemic are associated with the highest risk for developing olfactory dysfunction. This implies that a young female, who contracted an infection with the wild-type of SARS-CoV-2 was at highest risk of experiencing olfactory dysfunction. Conversely, individuals at an increased age, male gender, and those who experienced infection during a later phase of the pandemic were associated with the lowest risk for developing olfactory dysfunction. In current literature, it is reported that female gender is independently associated with long COVID syndrome, with females being 3.3 times more likely to develop it compared to males. Additionally, advanced age is linked to a higher risk for long COVID symptoms, with a 1.03 increased risk for every 10 years older (122).

Based on our findings, the status of immunity appears to play a role in the prevalence and duration of olfactory dysfunction in long COVID. Our study suggests that a higher percentage of vaccinated individuals, including those with natural immunity, reported no olfactory dysfunction compared to the unvaccinated group. The specific types of olfactory dysfunction were also less prevalent among the vaccinated group. Although the statistical significance was not reached in the analysis, there might be a potential association between vaccination status and olfactory dysfunction. Further investigation with larger sample sizes would be needed to better understand this potential association. Additionally, the analysis of

different combinations of vaccination status and olfactory dysfunction categories did not show a statistically significant association between the number of administered vaccine doses and the occurrence of olfactory dysfunction. According to a study investigating the protective benefits of vaccination, individuals who received two doses of COVID-19 vaccination before contracting SARS-CoV-2 had a 36% reduced risk of experiencing long COVID compared to those who were unvaccinated. However, the study did not find a significant difference in the risk of long COVID between those who received no vaccination and those who received only one dose. While the study didn't establish the protective effect of three or more doses, the findings indicate that receiving two doses of COVID-19 vaccination offers a higher level of protection against long COVID compared to no vaccination (123).

Based on our results, there seems to be a statistically significant association between the variant of concern and the prevalence of olfactory dysfunction. The likelihood of experiencing olfactory dysfunction appears to decrease as the VOCs of SARS-CoV-2 progressed from wild-type to omicron. These findings might indicate that the progression of the virus was accompanied by reduced virulence and fewer occurrence of olfactory dysfunction. In contrast to that, there is no statistically significant association between the duration of olfactory dysfunction and the phase of COVID-19.

Participants assigned to phase 1 (wild-type) had the highest percentage of olfactory dysfunction (47.6%), while phase 4 (omicron) had the lowest (14.3%). Regarding symptom duration, phase 1 showed the highest percentage of participants (27.0%) that experienced olfactory dysfunction for more than 12 weeks. In phase 4, not a single person reported a symptom duration for more than 12 weeks.

The Du et al. systematic review and meta-analysis found that the prevalence of anosmia in long COVID-19 varied depending on the strain of SARS-CoV-2. Specifically, in patients infected with the alpha variant, the combined prevalence of anosmia was 7.0%, whereas for those infected with the wild-type strain, it was 13.1%. Unfortunately, the study did not report the prevalence of anosmia in patients infected with the delta or omicron variant. The analysis included studies on patients with long COVID-19, regardless of their hospitalization status. The variation in the study population could potentially explain the lower percentages observed in our results. However, we also discovered a higher occurrence of olfactory dysfunction in patients with the wild-type variant compared to the alpha variant (124).

According to our data, there is no significant association between smoking or alcohol consumption and the prevalence of olfactory dysfunction. Statistical analysis conducted for both smoking and alcohol consumption indicate that any observed relationship between these

factors and olfactory dysfunction is likely due to chance rather than a meaningful connection. However, it's worth noting that the analysis didn't consider detailed factors such as smoking behavior and pack-years of smoking or the quantity of alcohol consumption, which could impact the results.

Regarding the association of olfactory dysfunction and other common clinical presentations of long COVID, we can identify several statistically significant relationships. We found that there is a strong association between olfactory and gustatory dysfunction. Analysis conducted across different phases consistently yielded significant p-values, indicating that the impairment of smell and taste often occurs together throughout the course of long COVID, more pronounced in the first phases. Furthermore, olfactory dysfunction has been found to have a significant association with headaches, implying that individuals experiencing olfactory dysfunction are more likely to experience headaches as well. Another symptom associated with olfactory dysfunction is tiredness. Similarly statistical significance was found in the association with tiredness, fatigue, and concentration difficulties. However, no consistent relationship was observed between olfactory dysfunction and memory difficulties in the provided data. The barely detectable statistical significance suggests that the association, if present, is not strong or consistent across different phases.

Research also indicates a strong correlation between the anosmia and ageusia in COVID-19 patients. A study conducted by Lechien et al. examined 2,581 patients with COVID-19-related smell impairment and found that 85.9% of them also experienced taste disturbances. This study provides evidence of the close connection between olfactory and gustatory dysfunctions in COVID-19 patients (125). Furthermore, individuals with long COVID frequently report additional symptoms such as headaches, memory difficulties, concentration problems, tiredness, and fatigue. In a study by Carfì et al., which followed up with 143 patients discharged from the hospital after COVID-19, 53% experienced fatigue, and 24% experienced cognitive impairment, among other symptoms (126).

Lastly, when examining weight loss in relation to olfactory dysfunction, no significant differences were found across varying degrees of olfactory dysfunction.

In contrast to that, studies have shown that prolonged smell and taste dysfunction, such as those experienced by individuals with COVID-19, can lead to a reduced desire and ability to eat and prepare food, leading to weight loss and nutritional insufficiency. Changes in appetite, altered perception of food's sensory properties, and decreased satisfaction after a meal can also contribute to changes in eating behaviors and body weight. While weight loss tends to be more prevalent, weight gain has also been reported in some cases (127).

5.1 Limitations

The cross-sectional survey study we conducted has provided valuable insights into the prevalence and characteristics of olfactory dysfunction in long COVID. Nevertheless, it is crucial to acknowledge the limitations inherent in our study design. These limitations can impact the interpretation and generalizability of our findings.

Firstly, our study faced limitations in terms of representativeness. The low response rate (14.3%) resulted in a relatively small sample size. Furthermore, the division of participants into smaller subgroups based on phases, duration, and symptom severity further reduced the sample size within each subgroup, compromising the representativeness of our findings. In some respects, subdivision resulted in loss of statistical significance.

In addition, slight differences were observed between responders and non-responders, particularly in terms of age and immunization status. This discrepancy may introduce bias and affect the generalizability of our results.

Secondly, comparing our study to others becomes challenging due to the high heterogeneity among studies. Variations in study designs, settings, populations, follow-up time, and symptom ascertainment methods introduce significant differences, making direct comparisons difficult.

Another limitation is the incomplete consideration of certain factors. We did not account for important variables such as children, ethnicity, preexisting comorbidities, and the severity of the initial and acute COVID-19 infection. The absence of these factors limits the comprehensiveness of our study and may result in an incomplete understanding of the impact of long COVID.

Given that all our participants were hospitalized, it is important to note that the applicability of these findings to the general population in Germany is constrained, as it implies a higher severity of infection.

A major challenge we faced was the lack of a clear and standardized definition of long COVID symptoms. Inconsistency in terminology, varying timeframes for symptom duration, and diverse categorizations of long COVID definitions in the literature hindered our ability to establish precise criteria for identifying and studying this condition.

Furthermore, the occurrence and epidemiological data of VOCs varied greatly across the world. This variability adds complexity to our findings, as we can only try to establish an understanding of how specific variants affected long COVID in Germany, or more specific, northern Bavaria.

It is important to note that the assignment of participants to a specific VOC was based exclusively on epidemiological prevalence rather than individual genetic sequencing of RT-PCR results. This approach may lack precision, especially during phases when multiple variants overlapped, leading to potentially incorrect assignment of participants, and therefore influencing our conclusions.

Our study is also susceptible to recall bias due to a time lag of up to two years between the initial COVID-19 infection and the survey participation. This gap in time might have influenced participants' recall of symptoms and their perceived severity, potentially introducing inaccuracies in reporting.

In addition, our study relied on subjective interpretation and self-reporting of symptoms. The absence of standardized clinical tests for symptom assessment introduces limitations in the accuracy and reliability of the data collected. In particular, the subjective distinction between loss of smell and taste is often confused and represents a major challenge in the assessment. Many patients cannot distinguish between taste and smell. This subjectivity introduces variability, making it challenging to establish clear distinctions between smell and taste dysfunction. Additionally, smell and taste are interconnected senses, often collaborating to create our perception of flavor. Issues in one sense can impact the other, making it difficult to pinpoint the exact source of dysfunction. Furthermore, there are overlapping symptoms, such as a reduced ability to detect flavors or a diminished perception of food aroma, which can be present in both smell and taste dysfunction, further complicating the differentiation process.

Subjectivity also plays a role in how tiredness and fatigue are interpreted and described. People may perceive tiredness differently, with one person labeling it as fatigue while another might not. Both tiredness and fatigue share overlapping symptoms, including decreased energy, difficulty concentrating, and a sense of exhaustion, making it difficult to differentiate them solely based on presentation. The underlying causes of both tiredness and fatigue depend on other factors, such as lack of sleep, physical and emotional stress, or preexisting comorbidities. Identifying the exact cause can be challenging since multiple factors contribute to both. Tiredness is usually transient and relieved by rest or sleep, while fatigue tends to be more persistent and can last for an extended period. However, duration alone may not be enough to distinguish between the two, as chronic conditions can lead to prolonged tiredness. Individual biases and variations in interpretation may further impact the validity of our findings.

Regarding the role of vaccination in the development of long COVID, we neither consider the type of vaccine, nor their specific variations in vaccine effectiveness against

different VOCs. These factors might also confound the analysis of symptoms and their association with vaccination.

While our cross-sectional survey study has provided valuable insights into long COVID and olfactory dysfunction, it is important to consider these limitations when interpreting our findings. To address these limitations, it is crucial to conduct larger prospective studies with matched control groups to directly attribute symptoms solely to COVID-19.

6. CONCLUSION

The study provided insights into the prevalence, severity, and duration of post-COVID symptoms, particularly olfactory dysfunction. The findings suggested potential associations between vaccination status, age, and the occurrence of olfactory dysfunction. The analysis suggests a trend where the likelihood of experiencing olfactory dysfunction decreases as COVID-19 variants progress from wild-type to omicron. However, further investigation with larger sample sizes and consideration of additional factors is necessary to establish conclusive relationships. The study highlighted the need for continued research on post-COVID complications to enhance our understanding of long-term effects and potential influencing factors.

7. REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33.
2. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2023 Jun 16]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
3. Bayerisches Landesamt Für Gesundheit Und Lebensmittelsicherheit, Koch-Institut R. Beschreibung des bisherigen Ausbruchsgeschehens mit dem neuartigen Coronavirus SARS-CoV-2 in Deutschland (Stand: 12. Februar 2020). 2020 Feb 13 [cited 2023 Jun 16]; Available from: https://edoc.rki.de/handle/176904/6487
4. Statista [Internet]. [cited 2023 Jun 16]. Coronavirus - Infektionen und Todesfälle in Deutschland. Available from: https://de.statista.com/statistik/daten/studie/1102667/umfrage/erkrankungs-und-todesfaelle-aufgrund-des-coronavirus-in-deutschland/
5. Corona-Zahlen für Deutschland [Internet]. [cited 2023 Jul 5]. Available from: https://www.corona-in-zahlen.de/weltweit/deutschland/
6. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic [Internet]. [cited 2023 Jun 16]. Available from: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic
7. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020 Feb 22;395(10224):565–74.
8. Yan L, Zhang Y, Ge J, Zheng L, Gao Y, Wang T, et al. Architecture of a SARS-CoV-2 mini replication and transcription complex. Nat Commun. 2020 Nov 18;11(1):5874.
9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270–3.
10. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019 Mar;17(3):181–92.

11. Karia R, Gupta I, Khandait H, Yadav A, Yadav A. COVID-19 and its Modes of Transmission. SN Compr Clin Med. 2020;2(10):1798–801.
12. Centers for Disease Control and Prevention [Internet]. 2020 [cited 2023 Jun 16]. Coronavirus Disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html
13. Centers for Disease Control and Prevention [Internet]. 2020 [cited 2023 Jun 16]. Coronavirus Disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html
14. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2021 Jan;224(1):35-53.e3.
15. Ma Q, Liu J, Liu Q, Kang L, Liu R, Jing W, et al. Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Dec 1;4(12):e2137257.
16. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239–42.
17. Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. Lancet Lond Engl. 2022 Oct 15;400(10360):1305–20.
18. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020 Mar 26;382(13):1199–207.
19. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–20.
20. COVID-19: Clinical features - UpToDate [Internet]. [cited 2023 Jun 16]. Available from: https://www.uptodate.com/contents/covid-19-clinical-features#H2249070035
21. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical

characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet Lond Engl. 2020 Feb 15;395(10223):507–13.

22. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet Lond Engl. 2022 Apr 23;399(10335):1618–24.

23. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul 1;180(7):934–43.

24. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020 Sep;7(9):e671–8.

25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061–9.

26. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 May 26;323(20):2052–9.

27. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020 May 22;369:m1966.

28. COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID") - UpToDate [Internet]. [cited 2023 Jun 16]. Available from: https://www.uptodate.com/contents/covid-19-evaluation- and-management-of-adults-with-persistent-symptoms-following-acute-illness-long-covid?search=long%20covid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

29. https://www.facebook.com/NIHAging. National Institute on Aging. 2020 [cited 2023 Jun 17]. Why COVID-19 testing is the key to getting back to normal. Available from: https://www.nia.nih.gov/news/why-covid-19-testing-key-getting-back-normal

30. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2020 Jan;25(3):2000045.
31. Chu DKW, Pan Y, Cheng SMS, Hui KPY, Krishnan P, Liu Y, et al. Molecular Diagnosis of a Novel Coronavirus (2019-nCoV) Causing an Outbreak of Pneumonia. Clin Chem. 2020 Apr 1;66(4):549–55.
32. Al-Hashimi OTM, Al-Ansari WIA, Abbas SA, Jumaa DS, Hammad SA, Hammoudi FA, et al. The sensitivity and specificity of COVID-19 rapid anti-gene test in comparison to RT-PCR test as a gold standard test. J Clin Lab Anal. 2023 Feb;37(3):e24844.
33. Böger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. Am J Infect Control. 2021 Jan;49(1):21–9.
34. Centers for Disease Control and Prevention [Internet]. 2020 [cited 2023 Jun 17]. Healthcare Workers. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html
35. Dinnes et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev [Internet]. 2021 Mar 24 [cited 2023 Jun 17];3(3). Available from: https://pubmed.ncbi.nlm.nih.gov/33760236/
36. Antigen and Molecular Tests for COVID-19 | COVID-19 Testing Toolkit [Internet]. [cited 2023 Jun 17]. Available from: https://covid19testingtoolkit.centerforhealthsecurity.org/testing-trackers/antigen-and-molecular-tests-for-covid-19
37. Snapshot [Internet]. [cited 2023 Jun 17]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html
38. Cheng MP, Yansouni CP, Basta NE, Desjardins M, Kanjilal S, Paquette K, et al. Serodiagnostics for Severe Acute Respiratory Syndrome-Related Coronavirus 2 : A Narrative Review. Ann Intern Med. 2020 Sep 15;173(6):450–60.
39. Fang FC, Naccache SN, Greninger AL. The Laboratory Diagnosis of Coronavirus Disease 2019- Frequently Asked Questions. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 Dec 31;71(11):2996–3001.
40. Kwee TC, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. Radiographics. 2020 Oct 23;40(7):1848–65.
41. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation,

and Treatment of Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/

42. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol. 2021 Mar;19(3):155–70.

43. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450–4.

44. Lai MM, Cavanagh D. The molecular biology of coronaviruses. Adv Virus Res. 1997;48:1–100.

45. Yang N, Shen HM. Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. Int J Biol Sci. 2020;16(10):1724–31.

46. COVID-19 (coronavirus disease 2019) - AMBOSS [Internet]. [cited 2023 Jun 24]. Available from: https://next.amboss.com/us/article/fI0kXh?q=covid+19#Y97feeba9fc7d4341827934ca8bf41ffd

47. Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells | Nature Communications [Internet]. [cited 2023 Jun 20]. Available from: https://www.nature.com/articles/s41467-020-17796-z

48. Escobedo RA, Singh DK, Kaushal D. Understanding COVID-19: From Dysregulated Immunity to Vaccination Status Quo. Front Immunol [Internet]. 2021 [cited 2023 Jun 20];12. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2021.765349

49. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 2021 May 1;97(1147):312–20.

50. Mehta P, Fajgenbaum DC. Is severe COVID-19 a cytokine storm syndrome: a hyperinflammatory debate. Curr Opin Rheumatol. 2021 Sep;33(5):419.

51. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Apr;8(4):420–2.

52. Diamond M, Peniston HL, Sanghavi DK, Mahapatra S. Acute Respiratory Distress Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 21]. Available from:

http://www.ncbi.nlm.nih.gov/books/NBK436002/

53. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526–33.

54. Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. The Lancet. 2022 Oct 1;400(10358):1145–56.

55. Tomashefski JF. PULMONARY PATHOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME. Clin Chest Med. 2000 Sep 1;21(3):435–66.

56. Hama Amin BJ, Kakamad FH, Ahmed GS, Ahmed SF, Abdulla BA, mohammed SH, et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. Ann Med Surg. 2022 Apr 6;77:103590.

57. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and Timing of Death in Patients With ARDS. CHEST. 2005 Aug 1;128(2):525–32.

58. Centers for Disease Control and Prevention [Internet]. 2023 [cited 2023 Jun 24]. COVID-19 and Your Health. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

59. Panchal U, Salazar de Pablo G, Franco M, Moreno C, Parellada M, Arango C, et al. The impact of COVID-19 lockdown on child and adolescent mental health: systematic review. Eur Child Adolesc Psychiatry. 2023 Jul 1;32(7):1151–77.

60. Runacres A, Mackintosh KA, Knight RL, Sheeran L, Thatcher R, Shelley J, et al. Impact of the COVID-19 Pandemic on Sedentary Time and Behaviour in Children and Adults: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2021 Oct 27;18(21):11286.

61. Centers for Disease Control and Prevention [Internet]. 2023 [cited 2023 Jun 24]. Understanding How COVID-19 Vaccines Work. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html

62. Mayo Clinic [Internet]. [cited 2023 Jun 24]. How do different types of COVID-19 vaccines work? Available from: https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465

63. Blanco J, Sarukhan A, Díez J, Bassat Q, Campins M, Brotons C, et al. Variant-adapted COVID-19 Vaccines. Where Are We? (10/10/22).

64. Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19 vaccines against

SARS-CoV-2 variants of concern: a systematic review and meta-analysis. BMC Med. 2022 May 23;20(1):200.

65. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. Radiology. 2020 Apr 7;201365.

66. COVID-19 Treatment Guidelines [Internet]. [cited 2023 Jun 24]. Hospitalized Adults: Therapeutic Management. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/hospitalized-adults--therapeutic-management/

67. Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, et al. Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nat Commun. 2021 Jan 12;12(1):279.

68. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020 Sep 15;324(11):1048–57.

69. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Nov 5;383(19):1813–26.

70. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med. 2021 Feb 11;384(6):497–511.

71. Amstutz A, Speich B, Mentré F, Rueegg CS, Belhadi D, Assoumou L, et al. Effects of remdesivir in patients hospitalized with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023 May;11(5):453–64.

72. Dexamethasone in Hospitalized Patients with Covid-19 - PubMed [Internet]. [cited 2023 Jun 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/32678530/

73. Marrone A, Nevola R, Sellitto A, Cozzolino D, Romano C, Cuomo G, et al. Remdesivir Plus Dexamethasone Versus Dexamethasone Alone for the Treatment of Coronavirus Disease 2019 (COVID-19) Patients Requiring Supplemental O2 Therapy: A Prospective Controlled Nonrandomized Study. Clin Infect Dis. 2022 Jul 1;75(1):e403–9.

74. Janus kinase inhibitors for the treatment of COVID-19 - PubMed [Internet]. [cited

2023 Jun 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/35695334/

75. Interleukin-6 blocking agents for treating COVID-19: a living systematic review - PubMed [Internet]. [cited 2023 Jun 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/33734435/

76. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial - PubMed [Internet]. [cited 2023 Jun 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/33734299/

77. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19 - PubMed [Internet]. [cited 2023 Jun 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/34351722/

78. Snapshot [Internet]. [cited 2023 Jun 29]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

79. Du M, Ma Y, Deng J, Liu M, Liu J. Comparison of Long COVID-19 Caused by Different SARS-CoV-2 Strains: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022 Nov 30;19(23):16010.

80. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. eClinicalMedicine [Internet]. 2023 Jan 1 [cited 2023 Jun 29];55. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00491-6/fulltext

81. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors Associated With Post−COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Intern Med. 2023 Jun 1;183(6):566–80.

82. Castanares-Zapatero D, Chalon P, Kohn L, Dauvrin M, Detollenaere J, Maertens de Noordhout C, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. Ann Med. 54(1):1473–87.

83. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. eClinicalMedicine [Internet]. 2022 Nov 1 [cited 2023 Jun 29];53. Available from:

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00354-6/fulltext

84. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 [Internet]. medRxiv; 2022 [cited 2023 Jun 29]. p. 2022.11.03.22281783. Available from: https://www.medrxiv.org/content/10.1101/2022.11.03.22281783v1

85. Boglione L, Meli G, Poletti F, Rostagno R, Moglia R, Cantone M, et al. Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect? QJM Mon J Assoc Physicians. 2022 Jan 9;114(12):865–71.

86. Aleem A, Akbar Samad AB, Vaqar S. Emerging Variants of SARS-CoV-2 and Novel Therapeutics Against Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK570580/

87. Read by QxMD [Internet]. [cited 2023 Jun 28]. Increased transmissibility of SARS-CoV-2 lineage B.1.1.7 by age and viral load. Available from: https://read.qxmd.com/read/34903718/increased-transmissibility-of-sars-cov-2-lineage-b-1-1-7-by-age-and-viral-load

88. Read by QxMD [Internet]. [cited 2023 Jun 28]. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Available from: https://read.qxmd.com/read/33723411/increased-mortality-in-community-tested-cases-of-sars-cov-2-lineage-b-1-1-7

89. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation - The Lancet Microbe [Internet]. [cited 2023 Jun 28]. Available from: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00068-9/fulltext

90. Read by QxMD [Internet]. [cited 2023 Jun 28]. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. Available from: https://read.qxmd.com/read/33761203/new-sars-cov-2-variants-clinical-public-health-and-vaccine-implications

91. Read by QxMD [Internet]. [cited 2023 Jun 28]. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Available from: https://read.qxmd.com/read/33684923/antibody-resistance-of-sars-cov-2-variants-b-1-351-and-b-1-1-7

92. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil | Science [Internet]. [cited 2023 Jun 28]. Available from:

93. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization: Cell Host & Microbe [Internet]. [cited 2023 Jun 28]. Available from: https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00183-9?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1931312821001839%3Fshowall%3Dtrue
94. Bericht zu Virusvarianten von SARS-CoV-2 in Deutsc.pdf [Internet]. [cited 2023 Jun 28]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/DESH/Bericht_VOC_2021-07-14.pdf?__blob=publicationFile
95. Zhan Y, Yin H, Yin JY. B.1.617.2 (Delta) Variant of SARS-CoV-2: features, transmission and potential strategies. Int J Biol Sci. 2022 Feb 14;18(5):1844–51.
96. Wöchentlicher Lagebericht des RKI zur Coronavirus-.pdf [Internet]. [cited 2023 Jun 28]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Wochenbericht/Wochenbericht_2022-11-10.pdf?__blob=publicationFile
97. Guo Y, Han J, Zhang Y, He J, Yu W, Zhang X, et al. SARS-CoV-2 Omicron Variant: Epidemiological Features, Biological Characteristics, and Clinical Significance. Front Immunol. 2022 Apr 29;13:877101.
98. Chen J, Wang R, Gilby NB, Wei GW. Omicron (B.1.1.529): Infectivity, vaccine breakthrough, and antibody resistance. ArXiv. 2021 Dec 1;arXiv:2112.01318v1.
99. Wochenbericht_2022-03-03.pdf [Internet]. [cited 2023 Jul 2]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Wochenbericht/Wochenbericht_2022-03-03.pdf?__blob=publicationFile
100. Anatomy, Head and Neck, Nasal Cavity - StatPearls - NCBI Bookshelf https://www.ncbi.nlm.nih.gov/books/NBK544232/#:~:text=This%20cavity%20is%20divided%20into,respiratory%20region%2C%20and%20olfactory%20region.
101. McKinley MP, O'Loughlin VD, Bidle TS. Anatomy & physiology: an integrative approach. 3e ed. New York, NY: Mcgraw Hill Education; 2019. 1 p.
102. Ercoli T, Masala C, Pinna I, Orofino G, Solla P, Rocchi L, et al. Qualitative smell/taste disorders as sequelae of acute COVID-19. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2021 Dec;42(12):4921–6.
103. Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. The Neuroscientist. 2021 Dec;27(6):582–603.

104. Mutiawati E, Fahriani M, Mamada SS, Fajar JK, Frediansyah A, Maliga HA, et al. Anosmia and dysgeusia in SARS-CoV-2 infection: incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms - a systematic review and meta-analysis. F1000Research. 2021 Jan 21;10:40.
105. Evolution of olfactory and gustatory dysfunctions in COVID-19 patients in India | SpringerLink [Internet]. [cited 2023 Jun 30]. Available from: https://link.springer.com/article/10.1007/s00405-020-06563-x
106. Prevalence of Olfactory Dysfunction with the Omicron Variant of SARS-CoV-2: A Systematic Review and Meta-analysis - PMC [Internet]. [cited 2023 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9774228/
107. Sudden and Complete Olfactory Loss of Function as a Possible Symptom of COVID- 19 - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32267483/
108. Loss of Smell and Taste in 2013 European Patients With Mild to Moderate COVID-19 - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32449883/
109. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32283006/
110. Expression of the SARS-CoV-2 Entry Proteins, ACE2 and TMPRSS2, in Cells of the Olfactory Epithelium: Identification of Cell Types and Trends with Age - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32379417/
111. Pathogenesis and transmission of SARS-CoV-2 in golden Syrian hamsters - PMC [Internet]. [cited 2023 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7394720/
112. Anosmia in COVID-19 Associated with Injury to the Olfactory Bulbs Evident on MRI - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32586960/
113. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19 - PubMed [Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/33257876/
114. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia - PubMed

[Internet]. [cited 2023 Jun 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/32937591/

115. Shamsundara M, Jayalakshmi L. Anosmia—An Effect of COVID-19 Infection-Review. Indian J Otolaryngol Head Neck Surg. 2023 Apr;75(Suppl 1):815–21.

116. Tan BKJ, Han R, Zhao JJ, Tan NKW, Quah ESH, Tan CJW, et al. Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modelling of recovery curves. BMJ. 2022 Jul 27;378:e069503.

117. Haseltine WA. Forbes. [cited 2023 Jul 5]. Loss Of Smell Linked To Long Term Covid Cognitive Impairment. Available from: https://www.forbes.com/sites/williamhaseltine/2022/08/09/loss-of-smell-linked-to-long-term-covid-cognitive-impairment/

118. Aberrant olfactory network functional connectivity in people with olfactory dysfunction following COVID-19 infection: an exploratory, observational study - eClinicalMedicine [Internet]. [cited 2023 Jun 30]. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00060-3/fulltext

119. Persistent post–COVID-19 smell loss is associated with immune cell infiltration and altered gene expression in olfactory epithelium | Science Translational Medicine [Internet]. [cited 2023 Jun 30]. Available from: https://www.science.org/doi/10.1126/scitranslmed.add0484

120. COVID-19 rapid guideline: managing the long-term effects of COVID-19 [Internet]. London: National Institute for Health and Care Excellence (NICE); 2020 [cited 2023 from: http://www.ncbi.nlm.nih.gov/books/NBK567261/

121. RKI - Archiv 2022 - Epidemiologisches Bulletin 38/2022 [Internet]. [cited 2023 Jul 10]. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/38_22.html

122. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2022 Apr 1;28(4):611.e9-611.e16.

123. Watanabe A, Iwagami M, Yasuhara J, Takagi H, Kuno T. Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis. Vaccine. 2023 Mar 10;41(11):1783–90.

124. Du M, Ma Y, Deng J, Liu M, Liu J. Comparison of Long COVID-19 Caused by Different SARS-CoV-2 Strains: A Systematic Review and Meta-Analysis. Int J

Environ Res Public Health. 2022 Nov 30;19(23):16010.

125. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2020 Aug;277(8):2251–61.

126. Carfì A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11;324(6):603–5.

127. Ferrulli A, Senesi P, Terruzzi I, Luzi L. Eating Habits and Body Weight Changes Induced by Variation in Smell and Taste in Patients with Previous SARS-CoV-2 Infection. Nutrients. 2022 Nov 29;14(23):5068.

8. SUMMARY

Objectives: The objective of this cross-sectional survey study was to investigate the prevalence, severity, and duration of post-COVID symptoms, with a specific focus on olfactory dysfunction. The study aimed to compare different virus variants of concern and explore potential associations between modifiable and non-modifiable risk factors and the prevalence or severity of symptoms.

Materials and Methods: The study involved former hospitalized patients at Coburg REGIOMED hospital, with data collected through a voluntary and anonymous survey. Participants were asked to provide informed consent. A comprehensive questionnaire collected demographic and health data related to their COVID-19 infection. Data collection was conducted through an online platform and remained accessible from September 2022 to December 2022. The dataset included survey responses supplemented with data from clinical records.

Results: The study population consisted of 1,025 participants, with a relatively balanced representation of males and females. The mean age for the entire population was 70.09 years. Significant variations in age were observed across different phases of the study. From the initial study population, 147 individuals participated in the survey, with a response rate of 14.3%. The demographics of the respondents were generally younger compared to non-respondents.

Regarding olfactory dysfunction, there was no significant association between gender and the sense of smell. Interestingly, we discovered a correlation between the virus variant and the occurrence of olfactory dysfunction. The prevalence of this dysfunction decreased as we moved from the wild-type variant to the omicron variant. The duration of olfactory dysfunction did not show a significant association with gender or the phase of COVID-19. However, there was a trend indicating that individuals without olfactory dysfunction tended to be older on average. Vaccination status showed a potential association with olfactory dysfunction, with a higher percentage of individuals without dysfunction in the vaccinated group. Smoking status and alcohol consumption did not significantly influence olfactory dysfunction.

There was a significant association between olfactory dysfunction and gustatory dysfunction. Associations were also found between olfactory dysfunction and concurrent symptoms such as headache, fatigue and concentration difficulties.

Conclusion: The study provided insights into the prevalence, severity, and duration of post-COVID symptoms, particularly olfactory dysfunction. The findings suggested potential associations between vaccination status, age, and the occurrence of olfactory dysfunction. However, further investigation with larger sample sizes and consideration of additional factors is necessary to establish conclusive relationships. The study highlighted the need for continued research on post-COVID complications to enhance our understanding of long-term effects and potential influencing factors.

9. CROATIAN SUMMARY

Title: Retrospektivna analiza u hospitaliziranih pacijenta uspoređujući različte varijante virusa SARS-COV-2 u svezi sa simptomom anosmije

Ciljevi: Cilj ovog presječnog istraživanja bilo je istražiti učestalost, ozbiljnost i trajanje simptoma nakon COVID-a, s posebnim fokusom na disfunkciju njuha. Istraživanje je imalo za cilj usporediti različite varijante zabrinutosti virusa te istražiti moguće povezanosti između promjenjivih i nepromjenjivih čimbenika rizika te učestalosti ili ozbiljnosti simptoma.

Ispitanici i postupci: Istraživanje je uključilo bivše hospitalizirane pacijente u bolnici Coburg REGIOMED, a podaci su prikupljeni putem dobrovoljne i anonimne ankete. Sudionici su zamoljeni da daju informirani pristanak. Opsežan upitnik prikupljao je demografske i zdravstvene podatke vezane uz njihovu COVID-19 infekciju. Prikupljanje podataka provodilo se putem online platforme i ostalo je dostupno od rujna 2022. do prosinca 2022. Skup podataka uključivao je odgovore na anketu nadopunjene podacima iz kliničke dokumentacije.

Rezultati: Istraživana populacija sastojala se od 1.025 sudionika, s relativno izbalansiranom zastupljenošću muškaraca i žena. Prosječna dob za cijelu populaciju bila je 70,09 godina. Primijećene su značajne varijacije u dobi između različitih faza istraživanja. Od početne populacije za istraživanje, 147 osoba je sudjelovalo u anketi, s stopom odgovora od 14,3%. Demografski podaci ispitanika bili su općenito mlađi u usporedbi s osobama koje nisu odgovorile.

U vezi s disfunkcijom njuha, nije bilo značajne povezanosti između spola i osjetila mirisa. Zanimljivo, otkrivena je korelacija između varijante virusa i pojave disfunkcije njuha. Učestalost ove disfunkcije smanjivala se kako smo prelazili s divlje varijante na omikron varijantu. Trajanje disfunkcije njuha nije pokazalo značajnu povezanost s spolom ili fazom COVID-19. Međutim, postojao je trend koji ukazuje da su osobe bez disfunkcije njuha na prosjeku bile starije. Status cijepljenja pokazao je potencijalnu povezanost s disfunkcijom njuha, s većim postotkom osoba bez disfunkcije u cijepljenoj skupini. Status pušenja i konzumacija alkohola nisu značajno utjecali na disfunkciju njuha.

Postojala je značajna povezanost između disfunkcije njuha i disfunkcije okusa. Također su pronađene veze između disfunkcije njuha i istovremenih simptoma poput glavobolje, umora i poteškoća s koncentracijom.

Zaključak: Istraživanje je pružilo uvid u učestalost, ozbiljnost i trajanje simptoma nakon COVID-a, posebno disfunkcije njuha. Rezultati su ukazivali na potencijalne veze između statusa cijepljenja, dobi i pojave disfunkcije njuha. Međutim, daljnje istraživanje s većim uzorcima i uzimanjem u obzir dodatnih čimbenika je potrebno kako bi se uspostavile zaključne veze. Istraživanje je istaknulo potrebu za kontinuiranim istraživanjem post-COVID komplikacija kako bi se poboljšalo naše razumijevanje dugoročnih učinaka i potencijalnih čimbenika koji utječu.