Diploma thesis

Long Covid – a synopsis of longterm effects on the basis of currently available medical data

A summary of pathophysiology, risk factors, symptoms and possible treatment concepts of post-acute Covid-19 syndrome and its impact on social structures

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Graz, 6th of August, 2025 *Anna Hernády m.p..*

Zusammenfassung

Long COVID, auch bekannt unter vielen anderen Namen, hat sich zu einer bedeutenden Herausforderung für die öffentliche Gesundheit entwickelt. Eine wachsende Zahl wissenschaftlicher Belege weist darauf hin, dass multisystemische Symptome weit über die akute Phase der SARS-CoV-2-Infektion hinaus bestehen bleiben. Diese Arbeit bietet einen umfassenden Überblick über den aktuellen medizinischen Kenntnisstand zu Long COVID und fasst zentrale Erkenntnisse zur Pathophysiologie, zu Risikofaktoren, klinischen Erscheinungsformen und therapeutischen Ansätzen zusammen. Auch die Auswirkungen von Long COVID auf soziale und gesellschaftliche Strukturen werden thematisiert und der Bedarf an weiterer Forschung entsprechend hervorgehoben.

Die Erkrankung betrifft eine sehr heterogene PatientInnengruppe. Zu den am häufigsten berichteten Symptomen zählen Erschöpfung, kognitive Einschränkungen (z. B. Gedächtnis- und Aufmerksamkeitsdefizite), Atemnot sowie kardiovaskuläre Auffälligkeiten. Frauen, Personen mit Vorerkrankungen und PatientInnen mit schwerem COVID-19 Verlauf sind überdurchschnittlich häufig betroffen, jedoch auch milde Infektionen können zu langanhaltenden Beschwerden führen. Das Ausmaß von Long COVID korreliert nicht mit der Schwere der ursprünglichen COVID-19-Erkrankung. Insgesamt wurden über 200 Symptome dokumentiert – was jedoch auch auf methodische Schwächen und ungenaue Einschlusskriterien der Forschung zurückzuführen sein könnte. Die zugrundeliegende Pathophysiologie gilt als multifaktoriell: Immunologische Dysregulation, virale Persistenz, endotheliale Schädigungen, Veränderungen des intestinalen Mikrobioms, Mikrothromben sowie autonome Funktionsstörungen scheinen eine Rolle zu spielen. Bestimmte Biomarker, wie erhöhte Entzündungswerte und veränderte Immunzellprofile, wurden mit einer anhaltenden Symptomatik assoziiert – jedoch fehlen bislang verlässliche prädiktive Marker.

Ein besonderer Fokus liegt auf den therapeutischen Möglichkeiten, die derzeit vorrangig symptomorientiert ausgerichtet sind. Zielgerichtete Behandlungsansätze existieren bislang nicht. Die Therapiestrategien umfassen multidisziplinäre Rehabilitationsmaßnahmen, symptomatische medikamentöse Behandlung sowie psychosoziale Betreuung. Immunmodulatorische Ansätze befinden sich aktuell in der klinischen Prüfung und könnten künftig eine vielversprechender Behandlungsoption sein.

Long COVID wirkt sich auch auf gesellschaftliche Strukturen aus – insbesondere auf Gesundheitssysteme, den globalen Arbeitsmarkt und die psychische Gesundheit.

Zusammenfassend stellt Long COVID ein komplexes und dynamisches Krankheitsbild dar, das interdisziplinäre Zusammenarbeit, patientenorientierte Versorgung und kontinuierliche Forschung erfordert, um Diagnostik, Therapie und gesellschaftliche Reintegration nachhaltig zu verbessern.

Abstract

Long COVID, also known as post-COVID-19 condition, has emerged as a major public health concern, with a growing body of evidence indicating persistent multisystem symptoms that continue well beyond the resolution of acute SARS-CoV-2 infection. This thesis provides a comprehensive overview of the current medical understanding of Long COVID, summarizing key findings in pathophysiology, risk factors, clinical manifestations, and therapeutic approaches. Long COVID's impact on social and societal structures will also be discussed, and the need for further investigation will be emphasized accordingly.

The condition affects a diverse patient population, with symptoms such as fatigue, cognitive dysfunction (e.g., memory and attention deficits), dyspnea, and cardiovascular irregularities most frequently reported. The syndrome disproportionately affects women, individuals with comorbidities, and those who experienced more severe acute disease, although even mild initial infections can lead to prolonged symptoms. The severity of Long COVID does not correlate with the severity of preceding COVID-19, and the wide range of manifestation includes over 200 reported symptoms. However, this could be due to fallacies in research and inaccurately defined research and inclusion criteria. The underlying pathophysiology is believed to be multifactorial, involving immune dysregulation, viral persistence, endothelial damage, changes in intestinal microbiome, microthrombi, and autonomic dysfunction. Certain biomarkers, such as elevated inflammatory markers and altered immune cell profiles, have been associated with symptom persistence, though specific predictive markers remain under investigation. Particular attention is paid to therapeutic options, remaining largely symptomatic and supportive, as no targeted treatments for Long COVID have been established to date. Strategies include multidisciplinary rehabilitation, symptomatic pharmaceutical interventions and mental health support. Immunomodulatory therapies are currently under investigation and may present a viable treatment for this syndrome.
Long COVID impacts social structures, from healthcare systems to employment and mental health services.

In conclusion, Long COVID represents a complex and evolving medical condition that requires interdisciplinary collaboration, patient-centered care, and continued research to optimize diagnosis, treatment, and social reintegration.

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Abbreviations

ACE-2 receptor	angiotensin-converting-enzyme 2 receptor
ADE	antibody-dependent enhancement
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AP	alkaline phosphatase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AT-2	angiotensin II
AT-2-cells	alveolar type 2 cells
BAL	bronchoalveolar lavage
BMI	body mass index
CARS	compensatory anti-inflammatory response syndrome
CCL	C-C chemokine ligand
CDC	Center for Disease Control (US)
CMV	cytomegaly virus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
DIC	disseminated intravascular coagulation
EBV	Epstein-Barr virus
ER	endoplasmic reticulum
ERGIC	ER-Golgi intermediate compartment
FIPV	feline infectious peritonitis coronavirus
GERD	gastro-oesophageal reflux disease
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
HHV-6	human herpes virus 6
HSV	herpes simplex virus
IBS	irritable bowel syndrome
ICU	intensive care unit
IFN-γ	interferon gamma
IL	interleukin
LRT	lower respiratory tract
LDH	lactate dehydrogenase
MCAS	mast cell activation syndrome
MCP-1	monocyte chemoattractant protein 1
MERS	middle east respiratory syndrome
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
MIS-C	multisystem inflammatory syndrome in children
NAD	nicotinamide adenine dinucleotide
NICE	National Institute of Health and Care Excellence
NFL	neurofilament light chain
NK-cells	natural killer cells
NSP	non-structural protein
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
ORF	open reading frame

PACS	post-acute COVID-19 syndrome
PCVS	post-COVID vaccination syndrome
PICS	post-intensive care syndrome
PNS	peripheral nervous system
POTS	postural orthostatic tachycardia syndrome
PRR	pattern recognition receptor
PTSD	post-traumatic stress disorder
RBD	receptor binding domain
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled study
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
RTC	replication-transcription complex
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRS	systemic inflammatory response syndrome
SpO2	oxygen saturation
TMPRSS2	transmembrane protease serine subtype 2
TGF-β	transforming growth factor beta
TNF-alpha	tumor necrosis factor alpha
UK	United Kingdom
URT	upper respiratory tract
US	United States (of America)
VEGF	vascular endothelial growth factor
VNS	Vagal nerve stimulation
VOC	variants of concern
VOI	variants of interest
vWF	von Willebrand factor
VZV	varicella zoster virus

Figures

Introduction

On the 31st of December 2019, the WHO's office in the People's Republic of China first picked up information about a cluster of cases of a new type of pneumonia in the area of Wuhan, China. The first cases of an unknown respiratory disease were reported in retailers of the Huanan Seafood Wholesale Market in Wuhan, though later on in the investigation process the epicentre of the following pandemic was revised (1). A previously unkown betacoronavirus was isolated from respiratory tract cells of infected individuals (2). In the course of the next few months, the spread of this novel coronavirus causing a disease named COVID-19 reached enormous proportions and was declared a global pandemic three months later, in March 2020 (3). Within only one year there have been over 256.8 million confirmed cases of Covid-19 and the pandemic caused more than five million deaths worldwide (4). SARS-CoV-2 causing *coronavirus disease 2019* (COVID-19) was not just posing a threat to the public health sector but was going to affect almost every sector worldwide and put countries, governments, companies and health institutions to a test. It infected a very large number of people in a short period of time, causing severe respiratory disease, significant chronic longterm implications and a large number of deaths because of high mortality rates in elderly and chronically ill patients. Additionally, not only COVID-19 itself but also the worldwide implicated pandemic measures to limit the spread of SARS-CoV-2 have had a severe impact on social structures and everyday life, resulting in increased numbers of mental illness. As a third, and primarily underestimated challenge to existing health care institutions, SARS-CoV-2 has a tendency to persist in certain patient populations and trigger a syndrome titled "Long COVID" or "Post-COVID condition", which can cause a variety of unspecific symptoms – limiting life quality to a great extent…

To understand the pathophysiology of Long COVID, a basic understanding of SARS-CoV-2 infection as well as COVID-19 is necessary. This thesis is set to summarize the wide range of clinical appearances of Long COVID Syndrome, as well as to discuss types of predictive markers, its impact on social structures and potential therapeutic options concerning this new disease.

1.1 SARS-CoV-2

1.1.1 Basic virology of SARS-CoV-2

SARS-CoV-2 is one of seven existing coronaviruses - enveloped viruses widely distributed among mammals and birds (2). Among them, SARS-CoV-2 is characterized by high transmissibility and increased pathogenicity (5,6). Three out of seven existing coronaviruses are linked to fatal illness in humans: SARS-CoV, MERS-CoV and SARS-CoV-2, leading to severe pneumonia with potentially deadly outcome (2). These three coronaviruses are likely to be zoonotic, having spilled over from animal reservoirs to humans (7). The family of coronaviruses was already discovered in 1937, as cause of viral bronchitis in birds. SARS-CoV-2 is believed to have originated from a spill-over from bats to humans via an intermediate mammalian host like the pangolin, as it shows a high similarity to the RBD of spike protein of Malayan pangolin coronavirus (5,6). Other sources also indicate an emergence of SARS-CoV-2 out of a type of bat-related coronavirus, as it shares up to 96% of its genomic sequences and is therefore phylogenetically more similar to this virus than to known human-related coronaviruses (8–10). Still, the suspected intermediate animal host of SARS-CoV-2 has not been discovered yet (1).

All Coronaviruses can be classified into four groups: Alpha-, Beta-, Gamma- and Deltacoronaviruses. While AlphaCoV and BetaCoV only infect mammals, GammaCoV and DeltaCoV mainly cause infections in bird species (4). They can all cause respiratory, enteric and neurological diseases in their hosts. Most coronaviruses are responsible for seasonal infections of the URT, presenting mild symptoms of the ‘common cold’. Betacoronaviruses on the other hand can lead to more serious disease and infections of the LRT, possibly even resulting in ARDS and extrapulmonary symptoms (2,11). SARS-CoV and MERS-CoV also belong to the family of Betacoronaviruses and have already caused pandemics in the past, but were not as highly transmissible as the newly discovered Betacoronavirus SARS-CoV-2, which has a lower mortality but is harder to detect due to its long incubation period and high rate of asymptomatic infections (1,4,9,12).

SARS-CoV-2 belongs to the kingdom of *Othornavirae,* the order of *Nidovirales*, family of *Coronaviridae*, subfamily of *Orthocoronavirinae*, genus of *Betacoronavirinae* and subgenus of *Sarbecovirus* (13). All Coronaviruses are positive stranded RNA viruses, showing a spherical shape with spike-like glycoproteins surrounding the surface, resembling its eponymous solar corona. The helically arranged nucleocapsid of SARS-

CoV-2 contains the largest genome of all RNA-viruses in a ss(+)-RNA configuration. It has six ORFs, the first (ORF1a/b) making up about two thirds of the genome. ORF1a/b encodes the non-structural proteins and is located at the 5'-end of the genomic helix. The ORFs that are located at the 3'-end encode the four essential structural proteins of SARS-CoV-2: the spike protein S, membrane protein M, nucleocapsid protein N and the envelope protein E (5,6,14). Figure 1 shows a simple sketch of the structure of SARS-CoV-2.

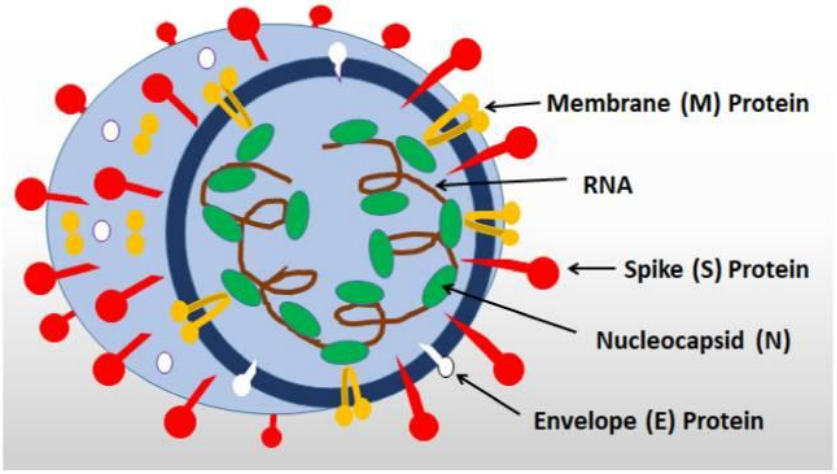

Figure 1 - The principal structure of SARS-CoV-2 (Gusev et al., 2022, p. 3)

The S-protein is responsible for identifying host cells that exprime the ACE-2-receptor (10). The transmembrane glycoprotein (4) is about 150kDa in size and mainly mediates attachment, fusion and viral entry into the host cell (5,15,16). It forms homotrimeric shapes standing out from the viral envelope, giving coronaviruses their name (8). This viral protein goes through conformational changes while interacting with ACE-2-receptor, ultimately enabling cell recognition and binding (10,15,17). It is therefore crucial for the infection pathway of SARS-CoV-2. S-protein can also be found on the surfaces of other viruses like HIV, Influenza and Ebola virus (4). It is built of two subunits: S1 and S2, which are cleaved by furine-like proteases of host cells (8,10). S1 is crucial in receptor recognition and binding, while S2 facilitates fusion of the viral and host cell membranes (4,6,16). Once inside the target cell, S-protein is able to trigger cell fusion between infected and healthy host cells, forming multinucleated giant cells and making host cells spread viral particles directly without being able to be neutralized by antibodies (5,14). By glycosylation of S-protein the virus is protected from host antibodies by concealing particular epitopes on the viral surface, which enhances host immune response evasion (4). Its significance concerning the infection pathway is supported by the fact that S-protein is also the viral antigen mainly involved in human immune recognition, induction of immune answer and neutralizing antibody production (9,18).

M-protein is the dominant structural protein and is essential for viral shape and envelope assembly, but it is also involved in a number of other steps in the lifecycle of SARS-CoV-2, as it interacts with all other structural proteins (4,6,8,14). M-protein is involved in virus maturation, nutrient intake, packaging and membrane budding (4,9). It is 25-30 kDa in size and determines the main outer structure of the virus. During the infection of host cells, M-protein and S-protein are interacting to ensure the incorporation of S-protein into the ERGIC (5), where the virus is retained in the ER. Through accumulating viral proteins, the ER can be overloaded, which can ultimately lead to cell death (4). It also interacts with N-protein to ensure the stability of the viral nucleocapsid and nucleic acid (8). For making up the final viral envelope, interaction with E-protein is also necessary.

E-protein is the smallest of all structural proteins with a size of 8-12 kDa and plays an important role in viral assembly, budding and subsequent release of virions (5,10) as well as pathogenesis (17). Through pores created in the host cell membrane by E-protein, the virions can be released from the cell (4). By its ability to form channels in membranes, it could contribute to the pathogenesis of COVID-19 by damaging epithelial barriers in the host (14). E-protein contributes to elevating the protein-folding load at the host cell's ER, which may lead to a state called "unfolded-protein response" and eventually cause host cell apoptosis caused by incorrectly folded proteins (6). Furthermore, it is involved in inflammasome formation during SARS-CoV-2 infection and therefore development of hyperinflammatory states, possibly contributing to emergence of cytokine storm (14). Its important function becomes apparent when taking a closer look at recombinant CoVs without E-protein: they show a significantly lower number of viral particles in hosts and immature viral particles. Also, E-protein is highly similar in different strains of CoVs and is mostly conserved throughout virus evolution (6).

N-protein is structurally bound to the viral RNA and is therefore essential for packaging of the nucleic acid, the structural organisation of viral particles and viral pathogenicity (5,8,17). It is also involved in viral transcription and replication and therefore has a high immunogenic potential (6). In the course of infection, this protein is produced extensively (4). N-protein is also associated with regulating host cell cycles and even inducing or preventing apoptosis, resulting in enhanced virus multiplication and spread (6,14). It interferes with host immune response like the interferon pathway and also promotes hyperinflammation in infected individuals (10,14).

The NSPs of SARS-CoV-2 are essential for multiple steps in its viral life cycle. NSP1 and NSP2 modulate host immunity by interacting with host ribosomes and human cell cycles

(6). NSP3 engages in NF-kB pathway signaling and hence plays a major part in the creation of cytokine storm in infected individuals. Other NSPs act as first cleavage proteins after successfully entering a host cell, and some are involved in processes like RNA synthesis, proofreading and modification. Additionally, the RNA of coronaviruses, including SARS-CoV-2, can form different types of secondary structures. These seem to affect the viral life cycle and function as regulatory elements as well as play an important role in the virus evolution (6).
The remaining ORFs encode another nine accessory viral proteins, which are assumed to play an important part in the modulation of and evasion from host immune response and host-virus interaction and are therefore determining viral pathogenicity and virulence (4,7,10). They will not be discussed further in the course of this diploma thesis.

The virus maintains its stability at airconditioned room temperature and is very resilient regarding different surface materials. High temperatures combined with elevated humidity seem to reduce the viruses' ability to spread. In comparison to SARS-CoV-1, novel-coronavirus-2019 has a higher basic reproduction number R0 and is able to spread faster and more efficiently (5).

1.1.2 Molecular pathophysiology and infection pathway

The life cycle of SARS-CoV-2 consists of 5 major steps: attachment, penetration, biosynthesis, maturation and release (4). It is shown by Figure 2 below. The process starts by binding of the virus to a host cell expressing its target receptor. Both pathogenic SARS-CoVs use ACE2-receptors as primary entry mechanism into target cells (14,15). But SARS-CoV-2 can additionally entry target cells via alternative routes, for example CD147, Neuropilin 1 or chondroitin sulfate (14,16). This partly explains the high contagiousness of SARS-CoV-2 and the wide range of infected tissues, as it has a variety of entry mechanisms when infecting a host individual and a broad tropism (14). Both SARS viruses need a host serine protease to start the viral replication cycle (by S protein priming) – in SARS-CoV-2 infections this is mainly mediated by TMPRSS2 (6,11,14,15). The results of Hoffmann et al support this finding, as inhibiting TMPSSR pharmacologically using camostat mesylate will inhibit infection of lung cells (15). They also found that SARS-CoV-2, like its relative SARS-CoV, can use cathepsin B and L for priming of S protein as an alternative (14,15). Three major cell types in human bodies were identified for co-expressing ACE2 and TMPRSS2 – type II pneumocytes, nasal goblet epithelial cells and

enterocytes. Unsurprisingly, these are the three tissues primarily infected by SARS-CoV-2 in human hosts (6).

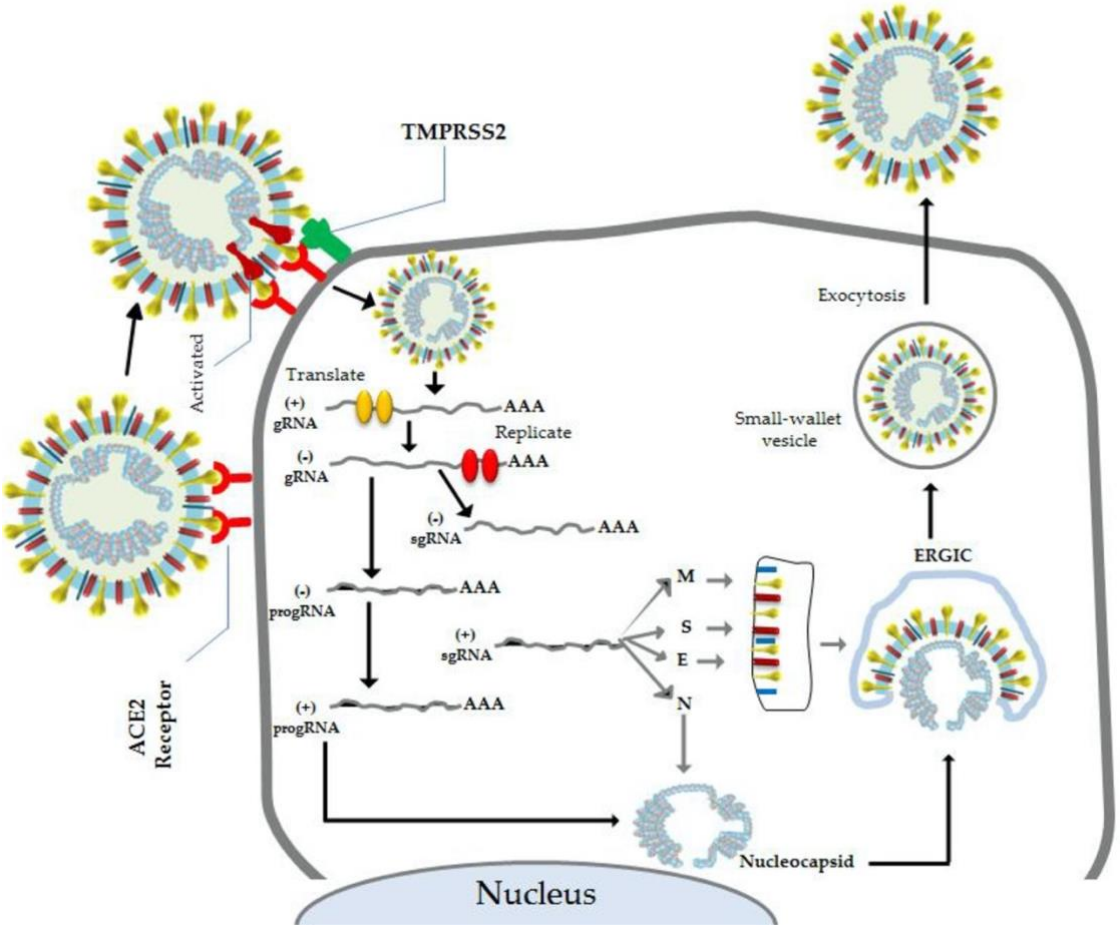

Figure 2 - Life cycle of SARS-CoV-2 (Astuti, Ysrafil, 2020, p. 410)

Like SARS-CoV, SARS-CoV-2 interacts with the ubiquitously available ACE 2-receptor, but because of a modified surface protein, the binding affinity of SARS-CoV-2 is higher - resulting in enhanced efficiency in host cell invasion (5,6,9,16). This may be an explanation for cross-species infection of SARS-CoV-2 (9). The binding process is induced by the interaction of the RBD of the S-protein with ACE2-receptors (6,16). The receptor-binding domain of S1 subunit binds to the peptidase of ACE-2 (5,14). By undergoing conformational changes, membrane fusion is triggered irreversibly and so, contact with the host cytosol is established (8,17). After entering the host cell, the process of uncoating is started (5) and the viral nucleic acid is released into the host cell (12,17). As already mentioned earlier, this process is especially started with TMPRSS2 (6,8,17). Following that, an RTC is formed by viral NSPs (6,10,16,17) and the viral RNA is

replicated (12). This replication process is majorly executed by the main viral protease and viral NSPs in SARS-CoV-2 (8,16), followed by protein translation using host tRNA (4,6). While the N-protein is mainly translated in the cytoplasm, the M-, E- and S-proteins are put together in the rough ER (4,12). The finished structural and accessory proteins are then released in the host cell's ER (6) and transported to the ERGIC (8,12). After finishing transcription and translation, the N-protein arranges itself around the synthesized RNA and forms the final nucleocapsid (4). The final step in the assembly of the virion is also facilitated at the ERGIC. This compartment releases the finished viral particles as vesicles and through secretary pathways they travel to the host plasma membrane (6,12,17), where they are released from the host cell by fusion with its plasma membrane called exocytosis (5,8,14).

The pathogenesis of SARS-CoV-2 infection has many potentially pathogenic mechanisms affecting the host individual. First, the virus is transmitted mainly by respiratory droplets or aerosols through talking, coughing or sneezing of infected individuals – symptomatic or asymptomatic (4). Even though SARS-CoV-2 has lower mortality rates than SARS-CoV and MERS-CoV, it is much easier transmitted and therefore poses a greater threat to public health (14). The likelihood of transmission increases with reduced air ventilation or enclosed spaces with reduced airflow, airborne transmission or transmission in open air is rather unlikely (18). As SARS-CoV-2 has a very firm protective outer shell and is rather resistant against external influences, it can persist in saliva and other body fluids. Furthermore, fecal transmission cannot be ruled out for SARS-CoV-2 (14). Transversal and perinatal transmission are also possible, but occur very rarely and are not associated with a compromised outcome of the newborn after birth (16). Before onset of symptoms, the median incubation period is 4-6 days but can last up to two weeks, depending on the patient's immune status (7,9,14,19). However, the highest infectivity is observed during the acute stage of SARS-CoV-2 infection, which is within 0-10 days after symptom onset due to the highest viral load in the febrile period of the infection. It reaches its peak on day 10, following a decrease in viral load due to seroconversion in the host (9). Increased ACE2 receptor expression may also play a role in infectivity, by indirectly increasing the intracellular viral load (9). Even though clinically ill patients are the primary source of infection, occult infections, asymptomatic and already recovering patients can be contagious as well (9). The viral load in some asymptomatic patients was even measured to be equally high to the viral load in clinically manifest SARS-CoV-2 infections (9). In the

case of airborne transmission, the cells primarily infected by SARS-CoV-2 are the multiciliated cells located in the nasopharynx, the trachea or cells of the nasal olfactory mucosa (7). Sungnak et al. found that ACE2 expression was the highest in nasal epithelial cells throughout the human respiratory system, particularly goblet cells or secretory cells and ciliated cells of the nasopharynx (20). If the virus cannot be eliminated in these cells of first contact, it spreads to the LRT by inhaling viral particles from the URT or by progressive spread along the tracheobronchial system (7). In the LRT, SARS-CoV-2 preferably infects type II alveolar cells (responsible for surfactant-production and lowering of surface tension) as they abundantly express the ACE2-receptor (7–9). Another discussed route of infection may be the fecal-oral transmission pathway, which appears to be seldom but could play a role in hospitals and clinics, as nosocomial SARS-CoV-2 infection (14,18).

The expression pattern of ACE-2 receptors throughout the human body helps to understand the variety of patient symptoms and the different manifestations of COVID-19. General symptoms of inflammation like fever, cough, headache and myalgia can be attributed to active virus replication in pneumocytes and other cells of lung tissue (5). By temporarily damaging the olfactory epithelium after inhaling viral particles and infecting the olfactory bulbus, it leads to olfactory dysfunction and loss of taste and smell (5). As the ACE-2 receptor is also expressed on endothelium, kidney, esophageal and intestinal tissue, different cell types of the heart, cholangiocytes and hepatocytes, urothelial cells of the bladder, the eyes, thrombocytes and macrophages, the testicles, the skin, adipose tissue, the thyroid and the nervous system (4,6,9), SARS-CoV-2 is able to infect these organs as well and can cause gastrointestinal, cardiovascular or renal symptoms (5,8). Invasion of these tissues can lead to multi-organ dysfunction or even failure and septic shock caused by SARS-CoV-2 infection (5). The most common manifestation is in the lungs and is explained by the large total surface area of alveoli, formed by type II pneumocytes which abundantly express ACE2 (4). Therefore, SARS-CoV-2 infection can also worsen preexisting respiratory diseases and bronchiolitis (11). Once infected, the LRT also suffers from more severe tissue damage than the URT, which manifests as rapidly developing ARDS in severely ill patients (9). The spread of SARS-CoV-2 to the lower lungs can be attributed to insufficient or effectively suppressed type I or type III interferon responses (7). As during SARS-CoV-2 infection ACE2 activity is restrained, this also triggers a dysregulation of the RAAS (4). ACE2 has indirect anti-infectious properties, which are consequently inhibited while active SARS-CoV-2 infection (18). ACE2 expression is

regarded as a protective factor for lung injury, and is downregulated by SARS-viruses (15). The main function of ACE2 in the human body is to convert angiotensin II into angiotensin (1-7), which inhibits the expression of proinflammatory cytokines including various interleukins, TNF-alpha and MCP-1 (18). Additionally, angiotensin (1-7) moderates the activation of several signaling pathways in infection (18). At the same time, angiotensin II triggers vasoconstriction and is a potent inducer of proinflammatory processes and increases cytokine production by recruitment of immune cells. Following an elevated amount of angiotensin II in SARS-CoV-2-infected individuals, an accumulation can lead to a dysregulation of the adequate immune response in the host, cardiovascular dysfunction, fluctuations of blood pressure, hypercoagulation through limited blood flow, and pulmonary remodelling processes resulting in fibrosis and renal damage (18).

The NIH categorizes symptoms into 5 grades of infection severity. Asymptomatic or presymptomatic infections are only detected by positive PCR-testing for SARS-CoV-2, as patients show no symptoms. Most patients with COVID-19 show signs of mild illness (7) like fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia or ageusia (21). By definition, shortness of breath, dyspnea or abnormal chest imaging are not present in these patients. Moderate illness includes evidence of LRT disease with a remaining SpO2 of $\geq$ 94% on room air. Severe illness is characterized by a SpO2 < 94%, a Horowitz-Quotient of < 300mmHg (PaO2/FiO2), a respiratory frequency > 30/min or lung infiltrates > 50% in chest imaging. Critical illness is the most severe possible manifestation of SARS-CoV-2 infection, including “respiratory failure, septic shock and/or multiple organ dysfunction” (21). The majority of patients present themselves with mild or moderate symptoms (about 40% of patients). Nevertheless, 15% of patients develop signs of severe illness and require oxygen therapy, and 5% even develop critical disease with systemic complications including respiratory failure, ARDS, sepsis or septic shock, thromboembolism or multiorgan failure (4). The most common symptom of severely ill COVID-19 patients is dyspnea. Patients developing dyspnea and hypoxemia soon develop progressive respiratory failure in the progress of the disease (7).

SARS-CoV-2 also has a direct impact on the immune system function. Innate immune response directly following infection is one of the most important mechanisms in the viral immune answer. It subsequently triggers other immune processes and an effective immune defense. Coronaviruses can suppress innate immune response in hosts (9).

After SARS-CoV-2 infection, CD4+ T-cells can mediate activation of B-cells and cytotoxic T-cells, inducing an immunological reaction. Specific IgG and IgM antibodies are produced and cytotoxic T-cells mediate direct neutralisation of the virus by engulfing infected cells. But even though immune response is induced shortly after, SARS-CoV-2 is likely to evade sufficient defense mechanisms by inducing T-cell apoptosis and leading to overwhelming and dysfunction of T-cells (11,14). Many SARS-CoV-2 infected patients show lymphopenia, with reduction of CD4- and CD8+-T-cells (9). Lymphopenia is witnessed more often in patients with severe COVID-19, while T-lymphocyte numbers can be normal in patients with mild cases of COVID-19 (18). Still, lymphopenia was included as diagnostic criterium of COVID-19, as it occurs frequently (9). Lower counts of T-cells are linked to enhanced SARS-CoV-2 dissemination and disease progression (22). In physiological immune response, IFN-I and IFN-III pathways as well as general pro-inflammatory stress are regulated upwards to prevent viral spread, called “primary IFN production” (14). Apparently, IFN-I and IFN-III have a protective function against developing COVID-19-associated pneumonia, especially when their response is triggered and timed appropriately (7). In SARS-Cov-2 infections, there is evidence that suggests a suppression of IFN-I and IFN-III immune response (11,14), which also enhances further infection, severe disease and hyperinflammation (7).

SARS-CoV-2, like many other viruses, has multiple strategies for the host immune-evasion. Directly after the host cell invasion, SARS-CoV-2 forms “replication factories from ER plasma membranes” (7), which shield the viral genome from detection by host PRRs by forming vesicles with double membranes to inhibit triggering of IFN production (7,9).

In addition to that, a total of eight viral proteins are able to avoid host immune induction through suppressing different IFN-pathways. The virus imitates host capping patterns of genetic code to escape recognition by host cells, and it is also capable of antagonizing different proinflammatory signaling pathways in host cells (8,9).

The impairment of IFN-I function is considered a key factor in the immunopathogenesis of critically ill COVID-19 patients (11). Following SARS-CoV-2 infection, the simultaneous activation of STAT3 and NF-kB pathways is triggered (two types of proinflammatory immune response pathways), and may lead to multiple autoimmune and inflammatory processes (11). A reduced number of B-lymphocytes, T-lymphocytes and NK-cells accompanied by a relative increase in CD8+-T-lymphocytes and neutrophils can be witnessed following viral invasion, as well as a dysfunction of T- and NK-cells (5,8,22).

Jimenéz and Arias on the other hand concluded, that while CD4+ and CD8+ T-cell numbers may vary in critically ill COVID-19 patients (they can be severely depleted as well as increased), their function is impaired and they show “elevated levels of activation and inhibitory receptors” (18). While inhibiting IFN pathways, coronaviruses enhance the production of other factors of innate immunity. This upregulation of inflammatory cytokines may be followed by an overshooting immune response called “cytokine storm”, triggering elevated production of pro-inflammatory substances like interleukins, CRP, TNF-α and fibrinogen. Increased fibrinogen levels are responsible for the hypercoagulable state during SARS-CoV-2-infection (5). SARS-CoV-2 interferes with a number of other immune response processes like oxidative stress, autophagy, lysosomal stress, protein ubiquination, mitochondrial stress, ER stress, expression of HSPs, cellular response to DNA damage and the formation of “a proinflammatory cell secretary phenotype” - all of which can induce or exacerbate cytokine production and result in a cytokine storm (14). In the course of a cytokine storm, an uncontrolled release of cytokines (e.g. IL-1, IL-6, IL-8, IFN-γ and TNF- α) and different chemokines occurs, which leads to hyperinflammation, inflammatory damage, ARDS and can ultimately lead to multi-organ failure and death (4,8,9).

The resulting combination of repressed innate and adaptive immune response and cytokine storm can cause severe pneumonia and inflammation, attacking type II pneumocytes in the host lung tissue and manifesting as ARDS (5). Especially the recruitment of different types of immune cells, mainly being T- and B-lymphocytes and macrophages, leads to diffuse alveolar damage and ARDS (11). DIC following a dysfunction of coagulation and increased IL-6 levels while simultaneously activating the coagulation cascade is a serious consequence worsening ARDS in patients, as multiple blood thrombi are formed in infected tissues. This might even lead to sudden cardiac death as cause of death (5).

It is strongly assumed that overshooting immune response and high proinflammatory mediators are responsible for severe cases of COVID-19, as they lead to tissue damage, impaired pulmonary function and complications in many parts of the body. In post mortem pathological specimens, the lung tissue of COVID-19 patients presented hyaline membrane formation, interstitial mononuclear inflammatory infiltrates, pneumocyte desquamation, microvascular thrombosis, diffuse alveolar damage and lung oedema (5,7,19). Mucus plugs, fibromyxoid and fibrinous exsudate in the lung tissue were also found because of inflammatory dysregulation and are a few of the defining pathological characteristics of COVID-19. Besides, at several sites of inflammation throughout the lung tissues of

deceased COVID-19 patients, no viral RNA was found. According to these findings, host inflammatory response is not directly linked to the presence of virus but rather induced by a delayed and dysregulated immune answer (18). This may explain critical symptoms even in younger patients. The pathogenesis of critical COVID-19 cases can therefore be explained by being the direct result of a dysregulated and over-activated immune host reaction (11,19).

1.1.3 Antibody-dependent enhancement following SARS-CoV-2 infection or vaccination

ADE is a phenomenon already known from viral infections like RSV or dengue virus and their vaccines (11,23,24), but also from different types of coronaviruses like SARS, MERS or FIPV (feline infectious peritonitis virus) in cats (23,25,26). It is defined as the process by which pre-existing antibodies against different serotypes of one virus lead to enhanced secondary infections (11,24). ADE has been shown in several in-vitro studies for different strands of SARS-CoV-2, which raised public concern prior to the development of the first effective vaccines (24–28). The investigated antibodies, derived mostly from healthy infected or vaccinated individuals, could be grouped into two main categories: high neutralizing activity antibodies and antibodies with poor neutralizing effects. The poorly neutralizing antibodies showed infection-enhancing properties in a variety of studies, while neutralizing antibodies were not shown to increase infectivity or disease severity (24,25). Liu et al, as well as other research groups, found an Fc-receptor-independent ADE mechanism in their in-vitro study, which means that enhancing antibodies can increase infectivity in host cells other than macrophages and monocytes carrying the Fc-receptor, during SARS-CoV-2 infection (25,27,28). However, the effect of ADE apparently depends on the host individual's distribution of effective neutralizing antibodies and poorly-neutralizing antibodies – as high levels of neutralizing antibodies prevent ADE in-vitro (23–26). Additionally, while the viral entry into host cells was enhanced during in-vitro experiments, this didn't correlate with increased viral replication or increased progression of disease in individuals in-vivo (23,24,27). In the study of Zhou et al, ADE showed a so-called "abortive replication", where macrophages are infected, but the viral replication cycle comes to a halt intracellularly and the infection process is not productive (24,27). Later conducted pre-clinical and clinical studies show, that immunisation prior to secondary infection doesn't negatively affect severity of COVID-19 in patients (24,26). Even though Yaugel-Novoa et al found higher rates of ADE in-vitro after receiving only

two doses of SARS-CoV-2 vaccines (infected with the Omicron variant), patient samples showed a trend towards lower ADE after receiving the booster-shot of the investigated vaccines (26). This findings are also supported by following studies on breakthrough infections in vaccinated individuals, in which pre-immunized individuals had a higher probability of developing asymptomatic or mild COVID-19 in comparison to unvaccinated subjects (24). There is no evidence of in-vivo ADE of SARS-CoV-2, as enhancing antibodies seem to trigger immunological answers in hosts and have a protective effect rather than affect disease severity (23,24,27). Nevertheless, in early stages of SARS-CoV-2 infection, ADE could still play a role in hosts with poor neutralizing antibody response, as plasma levels of enhancing antibodies may be connected to the severity of COVID-19 (25). On the other hand, Anti-N-protein antibodies belong to the poorly neutralizing group of antibodies, but N-protein still has a very high immunogenic potential, triggering an immune response. In mouse models, exposure to N-protein enhanced IL-secretion and increased lung injury. This could be an explanation for the phenomenon of cytokine storm in COVID-19 patients without active viral replication in macrophages or B-cells, as N-protein and anti-N-antibodies seem to aggravate the immune response and the inflammatory processes (24). Thus, it could be possible, that the phenomenon of ADE is connected to the development of Long COVID Syndrome, as said pathological findings in COVID-19 patients were also found in individuals suffering from Long COVID (24).

1.1.4 SARS-CoV-2 variants

In an attempt to prioritise between the high number of emerging virus mutations since the initial outbreak, SARS-CoV-2 strands have been classified as variants of concern and variants of interest, by comparing factors like viral transmissibility, virulence, reduced neutralisation by host antibody response, the evasion of virus detection and the decrease in the vaccine effectivity (5). SARS-CoV-2 is a virus with a high mutation rate, caused by a deficiency of mismatch repair mechanisms (4). As most of the mutations in SARS-CoV-2 come about in only one variant, genetic drift is suspected as the leading mutation cause (4). The most important VOIs are Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Kappa (B.1.617.1), Lambda (C.37) and Mu (B.1.621) (10). VOCs are similar to VOIs but additionally show increased transmissibility characteristics. They include Alpha (B.1.1.7), Beta (B.1.351, first detected in South Africa in 10/2020), Gamma (P.1, found in Brazil in 12/2020), Delta (B.1.617.2, first identified in India in 12/2020) and Omicron (B.1.1.529, detected in South Africa in 11/2021) – causing recurring waves of

COVID-19 infections worldwide (5). As these variants have ultimately developed because of the pressure of natural selection, the mutations have a direct impact on the virulence of SARS-CoV-2 and will bring forward new variants with varying characteristics in the future (10).

1.1.5 Epidemiology of SARS-CoV-2

As already mentioned above, the highest viral load is present in the URT of patients during the first onset of symptoms and the first week of the infection, which can be attributed to its higher infectious potential within the initial five days of symptomatic infection (5). The incubation period lasts from 5 to 14 days, while the number of asymptomatic infections is assumed to be around 30%. This contributes to the complicated tracking of infections (4). Generally, SARS-CoV-2 infected patients are infectious from day zero of the onset of symptoms or febrile phase of disease, but asymptomatic patients may be infectious as well (9). SARS-CoV-2 has a reproductive number R0 at around 2.2 (29).

The median age of symptomatic SARS-CoV-2 infection is around 50 years of age (16). Older and comorbid patients are more likely to develop clinical manifestations of COVID-19 after SARS-CoV-2 infection. Older age, higher SOFA-Score and D-dimers > 1µg/L are also associated with higher mortality rates (4), as well as immunocompromised patient groups (11). Higher age was associated with higher rates of ICU admission, invasive ventilation and fatal outcome with death (9). Some studies show that patients with cancer have a higher risk of contracting SARS-CoV-2 and are associated with poorer prognosis, as they fall into the immunocompromised group (9). Comorbidities with a higher risk of developing COVID-19 involve arterial hypertension, diabetes, chronic cardiovascular, renal and respiratory diseases, malignant diseases and obesity (4). While biological sex does not influence the probability of developing COVID-19, males are almost 2,5 times more likely to die of COVID-19 than females. This is suspected to originate in multifactorial causes including behavioural factors (4). Above the age of 60, the chances of respiratory failure, longer disease and greater severity of COVID-19 are increasing (16). It can be concluded that male sex, preexisting comorbidities and increasing age are the main risk factors for severe COVID-19 (7,16).

1.2 COVID-19

COVID-19 is the main disease caused by the pathogen SARS-CoV-2. At the end of 2024, over 281 million confirmed cases of COVID-19 were reported only in the European region (30). Worldwide, over 777 million cases have been reported, as well as 6.9 million deaths caused by COVID-19 since its outbreak in December 2019. Still, the real number of infections and deaths is believed to be higher (31). The spread of this disease was a challenge to health care systems around the world because it is characterized by high viral proliferation, high transmissibility and therefore high incidence rates and relatively high mortality rates (compared to other respiratory viruses). The combination of these characteristics put healthcare systems to a worldwide test.

Although most infected individuals have a rather mild course of disease and do not need hospital care, a small part of patients develop severe illness and require intensified medical care (31).

In May 2023, the WHO announced the end of the global COVID-19 pandemic, but SARS-CoV-2 and its consequences will accompany us for much longer, as some patients continue to suffer from clinical impairment long after the initial SARS-CoV-2 infection and viral clearance (31). This new medical condition titled “Long COVID Syndrome” or “Post-COVID condition” requires intense research and attention, to ensure early recognition and adequate treatment for a better patient outcome in the long run.

1.2.1 Epidemiology and diagnosis

The incubation period of COVID-19 ranges from 3-14 days, with a mean incubation period of around 3-7 days, depending on the source (7,19,29,32–34). Apparently, all ages, races and both sexes are susceptible to SARS-CoV-2 infection (34,35). The primary route of infection is, as already mentioned above, through person-to-person transmission by contact with fomites through infected secretions of the URT, respiratory droplets or aerosols of an individual, and by direct contact with infected mucosa (7,32,33). The fecal-oral route of infection cannot be ruled out, as viral particles have been detected in feces of infected individuals as well (33). The median age of infection is around 50 years, and the clinical manifestation can vary broadly depending on age and other risk factors, especially the patient’s immune status (32,35). Men and women are equally susceptible to the virus, but men have a higher risk of developing severe clinical courses, requiring admission to hospital for treatment and of death (35). Younger patients show a high incidence of asymptomatic infections or mild illness (35). As the percentage of asymptomatic infections

reaches up to 37%, transmission occurs easily without notice (33,36). Other sources report the number of asymptomatic or mild infections to be at 80% (29,33). Out of symptomatic patients, 40% develop mild symptoms, from which 80% are thought to be resolved on their own (36,37). Another 40% suffer from moderate symptoms, 15% develop severe illness manifesting as moderate pneumonia and 5% develop critical disease including ARDS, sepsis, septic shock, thromboembolism or multi-organ failure (29,36,37). The high rate of asymptomatic COVID-19-positive individuals may also be a consequence of the long incubation period (33). Additionally, the viral load is highest in the first few days following infection, thus in the asymptomatic period. Therefore, asymptomatic patients may be even more infectious and spread the virus quickly in the beginning of the disease without experiencing symptoms of their own (33). There is no evidence of enhanced risk of infection in pregnant individuals (35).

Besides male sex, other risk factors for severe courses of COVID-19 are > 60 years of age, smoking, unvaccinated individuals and people with comorbidities like hypertension, diabetes and obesity (7,19,33,35,38,39). According to Zizza et al., out of 26.650 patients in 72 studies, the most common comorbidities in COVID-19 patients were cardiovascular diseases including hypertension, and diabetes (33). Other sources also list hypertension and diabetes as most commonly prevalent comorbidities in patients requiring hospital care (37). The WHO lists following conditions as risk factors for developing severe COVID-19 on their data sheet: immunocompromised individuals, patients suffering from chronic diseases of the heart, the kidney, the lung, the liver or rheumatologic diseases, patients with HIV, diabetes, hypertension, an active cancerous disease, obesity, mental disorders, cerebrovascular diseases and dementia (31,36). Regardless of patient age, diabetes, cardiovascular diseases like hypertension, obesity, chronic diseases of kidney or liver, Parkinson's disease and cancer are independent risk factors of severity and death because of COVID-19 (22,32). According to the german S3-Guidelines for the Treatment of COVID-19, patients can be split up into three risk groups concerning the need for hospitalisation:

1. High risk (6%) – individuals after solid organ transplantation, anti-B-cell-antibody therapy, CAR-T-cell therapy and heavy immunosuppression
2. Intermediate risk (3%) – individuals above 65 years of age and/or with comorbidities like obesity, hypertension, diabetes, chronic diseases of the lung/kidney/liver, cancer, trisomy 21, and cardiovascular diseases.

3. Low risk (0,5%) – most patients, individuals without high or intermediate risk constellations (40).

Since obesity is linked to a chronic pro-inflammatory state with elevated inflammation markers, it could lead to a delayed and dysregulated immune response and therefore enhance viral reproduction following first pathogen contact (22). Worse clinical outcomes in elderly patients could be partly explained by the phenomenon of immunosenescence, which causes increased proinflammatory reactions and a reduction of antiviral cytokines (22). Apparently, individual vitamin-D levels and gut microbial dysbiosis also play a role in determining the clinical outcome after infection (38).

Research shows, that initially less than 20% of infected individuals developed severe COVID-19 (33). The onset of severe disease normally follows eight days after primary symptom development, while the mean time span until fatal outcome (like death or critical illness) is approximately 16 days (35). About 3-20% of patients with COVID-19 are in the need of hospitalisation, of which 10-30% require intensive care (7). Critically ill COVID-19 patients reach a mortality rate of almost 50% (4). Nevertheless, hospitalisation rates of infected individuals have declined steadily since the beginning of the pandemic – due to rising immunity through vaccines and lower virulence of the Omicron variant (40).

According to WHO data, a confirmed case of COVID-19 is defined by either a positive nucleic acid amplification test result (PCR) or by fulfilled clinical and/or epidemiological criteria and a positive SARS-CoV-2 antigen test result (41). All suspectedly infected patients should undergo testing to evaluate infection status, even if asymptomatic with history of contact with infected individuals. Antibody testing is not recommended by the WHO for diagnosis of current infection. However, antigen testing should be offered to the population for the possibility of self-testing.

The gold standard of detecting SARS-CoV-2-infected individuals is the molecular detection of viral RNA, mostly by RT-PCR (32,35,36,42). Even though the viral load is higher in the LRT, most tests are processed using samples from the URT by nasopharyngeal or oropharyngeal swabs, as they are easier to obtain (35). However, samples can be collected from sputum, bronchial fluid or blood as well (35). Data shows, that viral RNA can also be obtained from stool samples – in some cases even when respiratory samples or blood samples tested negative (32,35,42). Serological tests reacting to IgM and IgG antibodies against SARS-CoV-2 have been conducted in the course of the pandemic to identify previously infected and already recovered individuals, to quantify

immunity against SARS-CoV-2 in larger populations, as well as for collection of epidemiological data amongst countries and populations (32). Nevertheless, they are not suitable for confirmation of an infection, as antibody amounts may be too low to detect in the first days after infection (42). Antigen tests have proven a fast, cheap and low threshold alternative to time-consuming and relatively expensive PCR-testing methods. However, their sensitivity is comparatively low, and infection status should be confirmed by PCR testing in individuals with negative antigen test results and suspected infection.
In CT-scans of patients' lungs, ground-glass opacities (with or without interlobular septal thickening or consolidation) were the most frequently observed radiological characteristic of COVID-19. These are often bilateral, multilobular and showed a peripheral and caudal distribution in the lungs (19,35,43,44). Additionally, pleural effusion, lymphadenopathy and pneumonia-like bilateral infiltrates could be observed in chest CT scans of COVID-19 patients. In the early period of the pandemic, chest CT was helpful to quickly identify COVID-19 patients when other test capacities were overloaded or not available (19,35,43).

1.2.2 Pathophysiology of COVID-19

The course of a symptomatic SARS-CoV-2 infection can be split into an early infectious stage, a pulmonary stage and a hyperinflammatory stage (43). Directly after a person is infected, the virus replicates in the epithelial cells of the patient's URT, LRT, gastrointestinal mucosal lining or other sites of manifestation. In the majority of cases, the first tissue gaining contact to the virus is the nasal or tracheal multiciliated epithelium, which could explain anosmia as symptom. Like SARS-CoV, SARS-CoV-2 replicates in the cells of the nasal cavity and consecutively travels downwards along the airways directly or by deeply inhaling infectious viral particles (7,33). In this early infectious stage, only unspecific symptoms of the common cold are apparent, and viral invasion and replication takes place (43). Laboratory markers and blood counts are still normal in this stage (22). Entering the pulmonary phase of disease progression, a host immune response is triggered, which shows as typical COVID-pneumonia and with lung-specific symptoms (43,44). Only 15% of patients show signs of lower respiratory tract infection, yet if SARS-CoV-2 reaches the terminal airways responsible for gas exchange, it can cause progressive respiratory impairment and eventually failure due to direct damage to and apoptosis of the alveoli by viral replication and limited gas exchange (33,37). The infection of ciliated airway cells may inhibit ciliatory movement, which in turn enhances viral spread through impaired upward flow of mucus in the respiratory tract (7). In the hyperinflammatory

phase, a dysregulated immune reaction is triggered as the virus leaks into the bloodstream and can now infect other cell types throughout the body expressing the ACE-2-receptor (43). The caused tissue damage triggers a systematic inflammatory T-cell response and the recruitment of other inflammatory cells like granulocytes and macrophages. The result is a snowball effect of leucocyte recruitment, releasing of interleukins, cytokines and other inflammatory markers called “cytokine storm” (32,44,45). This stage of disease is accompanied by notable changes in the blood count and other laboratory markers. Normally, patients exhibit leukopenia, severe lymphopenia, slight eosinopenia, neutrophilia, thrombocytopenia in addition to elevated inflammatory markers like IL-6, CRP, ferritin, PCT and elevated D-dimers. The degree of deflection of the mentioned laboratory parameters correlates with disease severity – thus, inflammation parameters can be used for monitoring the course of the disease (22). Blood levels of IL-6, IL-8, and TNF at the time of hospital admission provide robust and independent prognostic indicators of patient survival (7). In lung tissue specifically, alveolar macrophages are recruited and AT-2 production is increased, which leads to pulmonary vascular permeability to augment acute phase response and immune reaction. The subsequent alveolar oedema leads to an impaired oxygenation and thus to hypoxia (19,29,45). High cytokine levels in the alveoli encourage T-cell apoptosis as well as apoptosis of respiratory epithelium and endothelium, which further amplifies viral replication and lung damage. This damage in turn causes vascular leak and aggravates oedema and results in hypoxemia and hypoxia (45). Furthermore, continuous stimulation by viral antigens induces functional exhaustion in $CD8^+$ T-cells, which can aggravate the cytokine storm and usually progresses to ARDS and other types of organ dysfunction (32,45). COVID-associated ARDS is dominated by diffuse alveolar damage in pathological specimens of the lung. This type of lung injury can be grouped into three categories or phases. In the first, the exudative phase, oedema, cell deterioration, hyaline membranes and inflammation are characteristic histological findings (7,44). This is followed by a proliferative or organizing phase, in which AT-2-cell hyperplasia occurs. Sometimes it is followed by a third, fibrotic phase, depending on disease duration and severity. In this final phase, septal fibrosis is characteristic in alveolar tissue (7). In other body tissues, cytokine storm triggers endothelial injury and tissue factor exposure, activating the coagulation cascade and resulting in hypercoagulability, thromboembolic events as well as increased bleeding risk from DIC (37). In the intestines, SARS-CoV-2 can lead to a disruption of the gut barrier. Through dislocation of bacteria and other pathogens from the gut into the blood stream, systemic inflammation is further

amplified (46). These factors together can impair almost any organ function throughout the human body. According to research, approximately one-third of COVID-19 patients show pulmonary embolism as direct cause of death, which suggests a high incidence of deep-venous thrombosis following hypercoagulable state in SARS-CoV-2 infection (18,19). The leading causes of death among COVID-19 patients are ARDS, severe viral pneumonia and multiple organ failure (32).

In individuals recovering from the disease, seroconversion usually takes place after 7-14 days after symptom onset. Following viral clearance, antibody titers persist at high levels for an extended period (22,45). It is still not clear weather and how the host antibody response might contribute to the development of COVID-19 or its sequel, Long COVID (22).

1.2.3 Clinical appearance and symptoms

The clinical appearance of COVID-19 can vary depending on the infected individual, comorbidities, affected organ system and risk factors. Normally, patients develop symptoms 5-6 days after infection which can last up to two weeks (31). According to the WHO, the most common symptoms are fever, cough, fatigue, anorexia, dyspnea and myalgia (36). Less common symptoms include heavy arms or legs, severe fatigue or tiredness, runny or blocked nose, sneezing, sore throat, headache, sore eyes, dizziness, new and persistent cough, tight chest or chest pain, hoarse voice, numbness or tingling, appetite loss, nausea, vomiting, abdominal pain, diarrhea, loss or change of sense of taste or smell and difficulty sleeping (31,34,36,47). Sometimes, COVID-19 can present itself with sputum production, rhinorrhea, confusion, hemoptysis, anorexia, liver damage and kidney damage (32,34,35,39,44,47). Other sources list dry cough, fever, chills, headache, fatigue or malaise, myalgia, dyspnea, diarrhea and other gastrointestinal symptoms as the most common clinical manifestations of COVID-19 (4,19,29,32–34,39,48). Clearly, the variety of symptoms is also dependent on the strain of SARS-CoV-2 causing the illness and can therefore differ slightly throughout medical scientific data. For example, the Delta variant is more likely to cause anosmia, while a sore throat is more common for infections with the Omicron variant (43). Anosmia and ageusia are the only pathognomonic symptoms, but it seems as if fever is a critical symptom, as it is listed constantly throughout literature and prevalent in almost all patients. As inflammatory processes in the respiratory tract irritate nerve endings responsible for the coughing reflex, many patients initially present

themselves with a dry cough (9,29,40). Patients with risk factors may additionally present with atypical symptoms including reduced alertness, reduced mobility, confusion and absence of fever (36). The majority of infected people do not develop severe or critical disease and only experience symptoms of the common cold and respiratory infection, as viral spread is limited to URT (7).
Even so, in some patients, SARS-CoV-2-infection leads to pneumonia and immunopathological symptoms of the URT and other organs (7). Severe cases of COVID-19 are usually defined by dyspnea as the primary symptom, which is caused by hypoxemia. Progressive respiratory failure is observed soon after the onset of dyspnea and hypoxemia in severe COVID-19. Affected individuals normally meet the ARDS criteria: severe hypoxemia and bilateral radiological opacities occurring within one week of exposure – NOT fully explained by fluid overload or heart failure. ARDS is characterized by pulmonary inflammation, increased pulmonary vascular permeability, and subsequent loss of ventilated lung tissue (7).

Critical disease in COVID-19 patients is defined by the WHO as disease with complications such as “respiratory failure, ARDS, sepsis, septic shock, thromboembolism or multiorgan failure (including kidney injury and cardiac injury)” (36). It affects around 5% of COVID-19 patients. As in other septic disease entities, coagulation abnormalities and dysfunction resulting in DIC can also occur in critically ill COVID-19 patients. DIC is also an important prognostic factor and can occur in up to 71% of patients with fatal outcome (44). Microthrombi and thrombi involving the lungs, extremities, brain, heart, liver, and kidneys have been reported in individuals with COVID-19 (45). About 30% of patients admitted to ICU developed ARDS within eight days after initial symptoms (7,39). Patients with severe symptoms of COVID-19 should receive appropriate treatment as soon as possible, as the consequences of the illness stretch from thromboembolism, respiratory failure and ARDS to sepsis, multiorgan failure and death (31).

Children can be infected by SARS-CoV-2, but very rarely develop lethal outcomes of COVID-19 (7). Even though children are less susceptible to SARS-CoV-2 infection because of a lower expression of the ACE-2 receptor, they can seldom develop a severe inflammatory response to infection after a couple of weeks (31,39). This serious illness is called multisystem inflammatory syndrome in children and adolescents (MIS-C) and is a delayed autoinflammatory process following SARS-CoV-2 infection. Although rare, it can

occur in response to COVID-19 and lead to multiorgan failure and shock. It is characterized by persistent fever, hypotension, gastrointestinal symptoms, lymphadenopathy, mucosal changes, rash and myocarditis and is similar to Kawasaki disease (14,36,45,49). The syndrome is a self-limiting vasculitis, eventually causing cytopenias, coagulopathy, coronary artery aneurysms, myocardial dysfunction and shock as a dangerous complication (45,49).

1.2.3.1 Pulmonary manifestation

Pulmonary manifestations of COVID-19 can be classified according to disease severity into three groups: non-severe, severe and critical (32,36). Non-severe illness can progress to more severe disease (32). In general, older populations develop severe courses of disease, complications like ARDS, multiple organ failure or death more often than young people (32). This may be due to the fact that the ACE-2-receptor expression is higher in the lung tissue of the elderly, as well as in the lung tissue of male patients and in fat tissue, which contributes to the higher incidence in men and obese patient groups (32).
WHO defines the criteria of disease severity of COVID-19 as following:
Non-severe cases of COVID-19 are defined by the absence of any criteria for severe or critical disease (36). These can be divided up into mild and moderate disease – mild being confirmed cases of COVID-19 without any signs of viral pneumonia or hypoxia, and moderate disease showing non-severe signs of pneumonia with an oxygen saturation above 90% on room air (36). In clinical practice they present themselves asymptomatic, with "body aches, cough, mild fever" or show mild pneumonia (32). Severe cases are defined by an oxygen saturation below 90% on room air (hypoxemia), severe pneumonia or signs of severe respiratory distress (32,36). Critical COVID-19 is defined by the criteria for ARDS, sepsis, septic shock or conditions that require intensive care unit admission with mechanical ventilation or vasopressor therapy (36).
ARDS can be divided into mild, moderate and severe ARDS, depending on the Horowitz-quotient. While healthy populations have a Horowitz-Quotient of > 300 mmHg, mild ARDS is defined by a Horowitz's quotient of 200-300 mmHg, moderate ARDS by a Horowitz's quotient of 100-200 mmHg, and severe ARDS by a Horowitz's quotient of ≤ 100 mmHg (36).

1.2.3.2 Extrapulmonary manifestations

As the ACE-2-receptor is abundantly expressed in cardiac tissue and endothelium, SARS-CoV-2 can also infect the cardiovascular system. COVID-19 can cause cardiac

manifestations either through direct damage of the virus on cardiac tissue but especially indirectly through the cytokine storm (32,37). SARS-CoV-2 binds to cardiomyocytes through the ACE-2-receptor and can directly cause damage to cardiac tissue (32). Cytokine storm and elevation of proinflammatory substances can result in myocardial damage with an increase of NT-proBNP and troponins, indirectly triggering heart dysfunction, manifesting itself as palpitations and chest tightness or pain, arrhythmia, hypertension and even heart failure (32,37,44). Following coronary vasospasm, hypoxic injury, microvascular thrombosis, direct endothelial damage, a general hypercoagulable state, and instability of atherosclerotic plaques, patients can present themselves with acute myocardial infarction or injury, myocarditis, pericarditis, vasculitis, cardiac arrhythmia or even heart failure as alternate cause of death in COVID-19 (19,37,39,44). The most common cardiac symptoms in COVID-19 patients are blood pressure elevation and palpitations. Paroxysmal atrial fibrillation is the most common type of arrhythmia in infected individuals. About 36,9% of ICU-patients showed significantly increased troponins in comparison to only 2,3% of not-critically-ill individuals (40). Even though COVID-19 patients admitted to the ICU sometimes showed signs of myocardial infarction like diffuse ST-segment elevations and high levels of pro-BNP, coronary angiographic examination didn't always show arterial obstruction (32,44). Myocardial injury and damage could also be a consequence of hypercoagulability in COVID-19 patients (44). The most common manifestation of COVID-associated coagulopathy is venous thrombembolism and pulmonary embolism, but cerebral venous thrombosis, arterial thromboembolisms, microangiopathy and DIC can also occur during the course of severe disease (44).

Additionally, underlying cardiovascular conditions and risk factors can lead to more severe clinical stages of COVID-19, eventually aggravating chronic cardiac diseases or causing an acute onset of a new cardiovascular illness. Patients suffering from arterial hypertension have a higher mortality risk than individuals without hypertension and also show elevated blood levels of CRP, IL-6 and PCT. Hypertensive patients under RAAS-blocker treatment showed a reduced intensity of inflammation (37). This concludes that hypertension may aggravate the chronic inflammation status in the course of SARS-CoV-2 infection.

Gastrointestinal symptoms occur in a significant proportion of COVID-19 patients. In some patients, the gastrointestinal symptoms were primarily present in the absence of clinical signs of pulmonary manifestation (44). As the ACE-2 receptor is also expressed in

mucosal tissue of the oesophagus, the stomach and the small intestine, viral overload can directly lead to nausea, vomiting, diarrhea, loss of appetite, abdominal pain and eventually even gastrointestinal bleeding (32,44). Additionally, liver and pancreas damage was also reported in some COVID-19 patients, presenting with elevation of liver enzymes as AST, ALT and AP, prolonged prothrombin time or high levels of LDH, lipase and amylase (32,44). About 14-38% of hospitalized COVID-19 patients showed an increase in liver parameters which correlated with the disease severity (40,44). It is still unclear if these signs of liver and pancreatic injury and occasionally occurring gastrointestinal bleedings are a direct result of viral damage or if they are a response to different medical therapies used in the combat of COVID-19.

The ACE-2 receptor is also expressed in renal tissue, and SARS-CoV-2 can cause direct renal damage by inducing proximal tubulus dysfunction (40). Yet, the kidneys may also be damaged in the course of systemic infection and cytokine storm, as they are very sensitive to changes in homeostasis (32). Acute kidney injury occurs in 1-29% of COVID-19 cases, and up to 56% of hospitalized cases (39,44). Acute renal tubular necrosis was found in histopathological autopsies of COVID-19 patients with fatal outcome (32). Preexisting chronic conditions of the kidney have been shown to be a risk factor of developing acute renal injury in COVID-19 patients. Also, the mortality risk is significantly higher in COVID-19 patients developing acute renal injury during the course of disease than in patients with normal renal function (32). This influential factor can be monitored by serum creatinine and urea nitrogen levels in the blood of patients (32).

Moreover, SARS-CoV-2 has a direct impact on neural tissue, as the ACE-2 receptor is also expressed in neurons and glial cells of the human brain. By direct damage through reactive astrogliosis and activation of microglia due to viral infection of neural tissue as well as through cytokine storm, immunological processes and hypoxemia caused by pneumonia, symptoms of the peripheral and central nervous system can ultimately be evoked (32,39,44). Prothrombotic condition during COVID-19 can cause further neurologic and psychiatric manifestations through microinfarcts and blood clots in the nervous system (50). Neurological manifestations occur in up to 80% of infected individuals, but are much more common in severely ill individuals and are associated with significantly higher mortality (30% in 30 days) (36,40,44). These can manifest in the CNS as headaches, dizziness, insomnia, change or loss of sense of taste and smell, neck rigidity, hemorrhagic

or ischemic stroke or infarction, ophthalmoplegia, ataxia, loss of peripheral muscle reflexes, changes in personality, agitation, aggression, cognitive impairment, delirium or encephalopathy, meningo-encephalitis, seizures and even decreased or loss of consciousness like coma (19,32,36,39,44,50). The most common neurologic symptoms were headaches and dizziness, which normally occurred shortly after infection. Other sources list anosmia (43%), dysgeusia (37%), weakness (30%), fatigue (38%) and myalgia (25%) (50). Reduced cognitive function was frequently associated with older age, severe infection, lower lymphocyte levels or higher CK-levels (44). Regarding the PNS, COVID-19 can cause polyneuritis, neuralgia, myalgia, weakness, fatigue, Miller-Fisher syndrome and rarely Guillain-Barre syndrome (44). Furthermore, COVID-19 can be accompanied by secondary psychiatric disorders such as anxiety, depression, sleeping disorders, agitation and posttraumatic stress disorder (36,44,50). Regarding mental health, anxiety, altered mental status and depressive symptoms are the most common manifestations in COVID-19 patients (36,50). Delirium is a relatively common psychiatric manifestation in severely sick patients, affecting up to 55% of COVID-19 patients in the ICU (50). Apparently, neurological and mental clinical manifestations of COVID-19 are associated with worse clinical outcomes and higher risk of severe progression of disease, with delirium especially increasing the mortality risk of patients with COVID-19 (36). In turn, premorbid psychiatric diagnoses do not increase the risk of developing COVID-19 (50). In fact, the use of antidepressants even seems to serve as protective factor against infection and COVID-19 (50).

The ACE-2 receptor is expressed in the basal lamina of the skin as well. Symptoms of the skin can include rashes, urticaria and erythema, though they mainly occur in mild or moderate cases of disease and precede respiratory affection in most cases (19,32). The causes could be related to direct tissue damage by the virus, as a consequence of cytokine storm or of antiviral drug therapy (32).

On top of that, ocular manifestations of COVID-19 have been reported (32). SARS-CoV-2 may even infect the eyes by direct contact, and SARS-CoV-2 was detected in human tears (33). When infected, after binding to the ACE-2 receptor in the conjunctiva or cornea, ocular pain and injection, foreign body sensation and conjunctivitis can occur in COVID-19 patients (19,32).

In conclusion, SARS-CoV-2 can infect a variety of organ systems and body parts. In some cases, clinical manifestations of COVID-19 have also been reported in the endocrine system, the reproductive system – especially in male patients – and the musculoskeletal system (32,39). It is therefore not merely a disease of the respiratory tract, but a multisystem disease which can even lead to multiorgan failure. The development of different types of symptoms depends on individual factors concerning immune response, comorbidities, average fitness, genetic factors and also other factors (32).

1.2.4 Treatment of COVID-19

Patient admission should be dependent on patient age, comorbidities, immune status, oxygen saturation and the respiratory rate (40). Mild cases of COVID-19 can be healed by symptomatic treatment and patient isolation, using antipyretics for fever and pain, adequate hydration and nutrition. Still, patients should be enlightened about probable complications of COVID-19, and encouraged to seek help when noticing these (36). As soon as a patient develops moderate COVID-19, symptoms should be monitored closely for signs of disease progression, in which case they should be admitted into hospital care (36). When admission to hospital is necessary in patients with severe COVID-19 pneumonia, initial laboratory diagnostics should contain CRP, LDH, AST, a differential blood count and D-dimers – these parameters should be monitored if needed (40). Also, oxygen saturation levels should be held above 94% and patients should be monitored closely (36).

In the beginning of the pandemic, treatment options mainly focused on best supportive care measures to mitigate severe courses of the disease – many of which are still relevant now. High flow oxygen therapy through nasal cannula and mechanical ventilation with orotracheal intubation may be necessary in cases of respiratory failure (7), as well as hemodynamic monitoring and support for septic patients. COVID-19 patients with signs of respiratory insufficiency should generally receive oxygen to ensure a saturation of SpO2 92-96%. For patients who develop ARDS, oxygen saturation should be monitored continuously as well as other vital parameters and parameters indicating disease progression (36). When PaO2/FiO2 falls below 100 mmHg, intubation and mechanical ventilation should be initiated with a tidal volume below 6mL/kg body weight (40). Furthermore, cautious fluid management and antimicrobial drugs for treatment of secondary infections are important (19,36). For patients with severe or critical disease,

blood cultures should be collected prior to antibiotic treatment (36). However, antibiotics should be given restrictively and only when signs of bacterial superinfection are present, (e.g. rising PCT or positive blood cultures) (40). When septic shock occurs in COVID-19 patients, the aimed MAP should be held ≥ 65 mmHg using crystalloid fluids and vasopressors, eventually (36).
In the hyperinflammatory stage of COVID-19, patients can benefit from anti-inflammatory therapies. As symptoms are mainly triggered by an overshooting immune response, immunomodulatory substances have proven to be efficacious in later stages of COVID-19 (40). Hospitalized patients receiving oxygen therapy showed better prognosis and reduced mortality with systemic corticosteroid therapy (22,43). Other sources show a reduction of mortality of 50% after administration of dexamethasone in patients with severe COVID-19 (7). Dexamethasone therapy should generally be offered to patients requiring oxygen therapy or with severe course of disease (e.g. 6 mg daily p.o. or i.v. for 10 days) (40). The IL-6-antagonist Tocilizumab can be used additionally (dosage depending on body weight) if patients show rapid disease progression or respiratory failure. Data shows increased survival of hospitalized COVID-19 patients receiving Tocilizumab (7,40). Inhaled corticosteroids should not be used for COVID-19 patients, as they showed no benefit (40). Coagulopathy among COVID-19 patients can be treated with low molecular weight heparin or fondaparinux. Anticoagulation has even shown to reduce hospital mortality rates and intubation frequency (7,22). Anticoagulation should not be given by default, it is only recommended for hospitalized patients or immobile individuals (40). During the whole hospital stay, the WHO recommends regularly “monitoring patients for thromboembolism such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome” (36).

Nevertheless, antiviral medication has been developed by now. Since symptoms in early stages of viral infection can be attributed to direct damage by viral replication inside the host tissue, antiviral therapy is only effective within a very early phase of disease (normally 5-7 days after symptom onset) (7,40). After that timespan, antiviral substances are unlikely to have a significant effect on the patient outcome, as the virus has already spread and triggered systemic immunopathology (7). The german guidelines explicitly recommend using antiviral treatment for COVID-19 patients with high risk of hospitalisation within the first seven days of symptom onset. Nirmatrelvir/ritonavir and remdesivir are currently available as oral and intravenous options of causal therapy (40).

Nirmatrelvir/ritonavir – known as paxlovid – is an oral drug for the treatment of mild to moderate COVID-19 (32). It consists of a protease inhibitor and a CYP-450 inhibitor, which is why interactions with other drugs are a major side effect, and it's use should be weighed out carefully (32). Still, paxlovid has shown to substantially decrease the severity and mortality mainly in elderly patients (32). There is an evidence-based recommendation for use of paxlovid 400 mg 2x/day orally within first five days of symptom onset for five days (40). Remdesivir is an intravenous option for direct antiviral treatment of COVID-19. It is also recommended within the first five days of symptom-onset. A dosage of 200 mg i.v. on day 1 and 100 mg i.v. daily from day two onwards should be administered to high-risk patients, patients with COVID-19-pneumonia or patients requiring low-flow oxygen therapy for 3-10 days, depending of clinical presentation (40). Immunocompromised patients with persisting SARS-CoV-2 infections should even receive antiviral combination therapy (40).

In palliative care, symptomatic therapy is ethically required. The german guidelines make a strong recommendation for palliative treatment to ease dyspnea, anxiety, rattle breathing and delirium. Dyspnea should be treated with opioids, anxiety with benzodiazepines, rattling breath with anticholinergic medication and delirium with antipsychotics (40).

Still one of the most important precaution measures is the isolation of infected patients – in hospital care as well as in outpatient settings. The WHO and the german S3-guidelines recommend immediate isolation of patients, making no difference between suspected, probable or confirmed infection status of the person concerned (36,40). People with negative test results should be isolated for five days, people tested positive should be isolated for ten days to prevent the spread of infection (36). Rapid antigen tests can be used for follow-up to reduce the period of isolation (36). Asymptomatic patients can be released from isolation seven days after retrieving the positive test sample, mild cases after seven days after primary onset of symptoms. Moreover, adequate and frequent ventilation of enclosed spaces should be ensured (40). Other basic measures to prevent the spread of disease are the use of face masks and personal protective equipment, frequent hand hygiene, disinfection of contaminated surfaces and medical equipment, usage of gloves for patient contact and avoiding touching eyes, nose and mouth (36,40). Screening for early recognition of suspected cases should be implemented at first point of contact with the local health care system as well (36).

1.2.4.1 COVID-19 vaccines

There are many different vaccines from different countries and companies currently available against developing severe cases of COVID-19 – with varying efficacy and side effects. Although the vaccines have proven to be effective against the development of severe COVID-19, it may have led to outbreaks of increasingly contagious variants of SARS-CoV-2 (43). Even though there is ambivalent data towards the currently available vaccines, the WHO still advocates COVID-19 vaccinations as preventive measures against developing the disease. Especially groups with higher risk of severe illness like people aged > 60 and with underlying chronic diseases, pregnant and completely unvaccinated individuals should consider getting a vaccination, as they prevent serious illness, hospitalisation and death (31). Nevertheless, current data is emerging, showing a decreasing immunity against COVID-19 with an increasing number of booster vaccines received. Repeated vaccination with the same antigen has been associated with immune exhaustion, characterized by overstimulation of $CD4^+$ T cells and the emergence of autoreactive $CD4^+$ T cells capable of inducing autoantibody production, thereby diminishing protection against future infections (38). Evidence has already demonstrated that vaccine-induced immune imprinting against the spike (S) protein can partially suppress the immune response to the nucleocapsid (N) protein following SARS-CoV-2 infection (38). Side effects of COVID-19 vaccines mostly include mild to moderate adverse effects, like “pain at the site of injection, fever, chills, muscle pain, joint pain and headaches” (38). Prolonged adverse effects following administration of currently available COVID-19 vaccines are increasingly being identified and examined, remaining for weeks or even months (38). Some of these side effects resemble COVID-19 as well as Long COVID symptoms. They are reaching from cardiovascular, neurological and autoimmune to inflammatory manifestations – these can be summarized under the term “post-COVID-19 vaccination syndrome” or “PCVS” (38). Fatigue, neuropathy, brain fog and headaches occur as symptoms of Long COVID and of PCVS, while dysgeusia and anosmia are more common in post-COVID condition (38). Thus, a vaccination (especially regular booster shots) should be carefully weighed up against side effects and be discussed together with the patient.

1.2.5 Progression and prognosis

Most patients admitted to hospital because of COVID-19 can be released home after two weeks following sufficient recovery (35). The need of hospitalisation has dropped drastically throughout the past few years. Initially, around 30% of hospitalized patients developed ARDS, and 13,9% showed fatal outcomes. These numbers have dropped to below 14% of necessity of hospitalisation in Germany – which can be compared to western and middle European standards and numbers (7,9). Most severely ill patients showing signs of cytokine storm and neutrophilia as well as an increase in the neutrophil/lymphocyte ratio are associated with poorer clinical outcome and/or complications (45). These include microthrombi and thrombosis, cardial arrhythmia, bacterial superinfection, myocardial injury, acute kidney injury and multiorgan dysfunction or failure (40). Other factors like thrombocytopenia, elevated D-dimer levels, high levels of CRP, ferritin and PCT and defective coagulation are linked to poor or fatal clinical outcome as well (7,22,45). Especially high levels of IL-6 have been associated with an increased mortality (22). Hyperinflammation is therefore considered to be one of the most important prognostic biomarkers in critically ill COVID-19 patients (22).

Because of diverse prothrombotic factors during severe COVID-19, patients also have a significantly higher risk of venous and arterial thrombosis than healthy individuals. In a metaanalysis of around 64000 COVID-19 patients, the prevalence of thrombotic events in ICU-patients was 23%, compared to 9% of COVID-19 patients in general (43).

Acute kidney injury in COVID-19 patients is also associated with higher morbidity and mortality. Therefore albuminuria, hematuria and leukocyturia should be ruled out by a urine check of hospitalized patients (40). As chronic liver diseases are a risk factor for death following COVID-19, patients with elevated liver enzymes should be examined for the presence of hepatitis infections and drug-induced liver injury (40). Another factor associated with poorer clinical outcome and increased risk of mortality is delirium (36).

Following invasive mechanical ventilation, patients may suffer from further lung injury caused by barotrauma and oxygen toxicity. Pneumothorax and pneumomediastinum are the most common side effects of ventilation therapy in COVID-19 patients (43). The use of immunomodulatory drugs on one the hand and a severely dysregulated immune system on the other hand can cause superinfections like influenza, aspergillosis or mucormycosis, further worsening clinical outcomes and mortality rates in critically ill individuals (43).

Furthermore, post-intensive-care-syndrome is a serious and frequent complication after

severe COVID-19. It is characterized by paralysis, cognitive and psychological impairment following prolonged intensive care and can theoretically occur after any ICU-stay (38,40). After recovering from COVID-19, most patients have some protection against breakthrough infections for a certain period of time. However, breakthrough infections do occur after recovery or after vaccination. Women, adults, immunocompromised people and previously hospitalised patients have a higher risk of experiencing repeated SARS-CoV-2 infections (43).

1.3 *Long Covid – an urgent need for understanding an emerging disease*

Some patients experience prolonged symptoms after a SARS-CoV-2 infection – regardless of whether they needed hospital care or not. This condition is known as Long COVID, post-acute COVID-19 syndrome (PACS) or post-COVID condition and normally occurs a few months after acute COVID-19 or SARS-CoV-2 infection (31,36). In the course of this diploma thesis, it will be referred to as Long COVID or post-COVID condition.

Due to the great percentage of COVID-19 patients still exhibiting symptoms long after recovery, the german guidelines even suggest screening hospitalised COVID-patients for persisting symptoms 8-12 weeks after hospital discharge (40). Even though more and more data concerning Long COVID has been collected and shared across the globe, there is still a very urgent need for a better understanding of this complex syndrome. As shown throughout the introduction, the causing virus infection SARS-CoV-2 and the subsequent disease COVID-19 are very complex and multisystemic entitites on their own. Long COVID presents itself with an equally wide range of symptoms and (currently) fewer therapeutical options. Additionally, many health care workers and doctors are not familiar with clinical symptoms, physiopathology, prognostic markers, treatment and rehabilitation options of this new disease, which is why they easily feel overwhelmed and helpless when tending to Long COVID-patients. The consequences are a delayed diagnosis, limited or no access to specialised centers, suboptimal or incorrect treatment, and, overall, inadequate medical care for affected individuals.

The aim of this thesis is to find a uniform definition of the disease of Long COVID, summarise the key points of its clinical appearance, point out possible diagnostic and prognostic parameters for disease monitoring and progression control as well as to discuss the most important therapeutic options of treating this illness. Additionally, possible

longterm effects of not reacting adequately to this emerging disease and sociodemographic differences in clinical and diagnostic measures should be discussed. Ultimately, a better global understanding of long COVID should be achieved, helping health care professionals to develop a sufficient competence when it comes to recognizing, diagnosing and treating post-acute COVID-19 syndrome…

2 Materials and Methods

A review of literature published in the past five years (2021 until 2025) was done in order to gather information on SARS-CoV-2, COVID-19 and Long COVID syndrome. A broad understanding of the underlying infection and disease is important and necessary to comprehend the pathophysiology of Long COVID. Therefore, an overview of these two entities was given throughout the introduction of this thesis to ensure a general understanding of the subject. Search queries were limited to english publications, except the german guidelines for COVID-19 and Long COVID, which were also used in the course of this thesis. Literature research was mainly conducted on the PubMed, but also on Science Direct and Google Scholar, and was limited to reviews, books, systematic reviews, metaanalyses and clinical studies on humans. Additionally, public information of institutions like the WHO, the NIH or the CDC, international as well as local guidelines were used as sources of information. In the course of my research, I attended one online conference covering Long COVID, potential biomarkers and therapeutic options, called "Unite to Fight 2024" in May 2024. A transcript of this conference was also used as literary source and is attached to this thesis in the appendix.

The first database search was conducted on the 26th of March 2024 searching the MesH database for the terms "SARS-CoV-2" and "physiology", "growth", "development", "classification", without the term "vaccination". Another search query was done using the terms "structure", "infection pathway" and "molecular biology" in combination with "SARS-CoV-2".

A second literature search was conducted on the 3rd of January 2025, mainly focusing on COVID-19 and Long COVID. The terms used were "COVID-19" and "classification", "diagnosis", "epidemiology", "physiopathology", "symptoms" or "clinical appearance", "therapy" or "treatment" or "rehabilitation", "prognosis" or "progression". In another round the same secondary search terms were used for the "Long COVID" filter in the PubMed, including "definition" and "mortality" as keywords. To increase sensitivity during research, the MeSH-Term post-acute COVID-19 syndrome was also included in the second literature search. Additionally, current treatment guidelines and information from the WHO website were constantly checked and updated during the writing process.

In total, 97 pieces of literature were included into the source list of this thesis, with 70 being scientific literature pieces from different journals, three guidelines concerning clinical handling of the different entities, and the rest being multiple online entries from the

WHO official website, the CDC's official website and the International Committee on the Taxonomy of Viruses.

3 Results

Millions of people worldwide are fighting with prolonged illness and recurring symptoms after initial SARS-CoV-2 infection – ranging from severely ill to mild to even asymptomatic patients (51). The respiratory, endocrine, cardiovascular, neurological, autonomous and immune system are just some of the most common sites of manifestation (52). This multidimensional disease has been called Long COVID by affected patients, and inflicts medical, economic and social problems on human civilisation around the world (53). For affected individuals, it is especially debilitating, as it severely impairs life quality and activities of daily life (51). It occurs in up to 45% of COVID-19 survivors (54). Finding a definition for this emerging disease is not a simple task. Multiple different definitions have been postulated which differ from each other concerning duration and onset of the illness, patients in- or excluded in studies and over 200 different symptoms associated with Long COVID all in all. Researchers have used inconsistent ways of classifying types of Long COVID – according to clinical presentation, symptom duration and time of appearance or the severity of Long COVID (38). No clear pathophysiological pathway for Long COVID has been found, neither have been pathognomonic biomarkers for this disease. This makes collecting and finding data on the topic much more difficult and even harder for affected institutions and individuals to understand and study post-COVID condition.

3.1 Defining Long COVID

The term Long COVID itself has been primarily used by patients affected by persisting symptoms, as there was no official name for this disease yet. Throughout the pandemic, terms like "long-haul COVID", "post-COVID syndrome (PCS)", "post-acute COVID-19 syndrome (PACS)", "chronic COVID", "post-acute sequelae of SARS-CoV-2 infection (PASC)", "post-COVID-19 condition", "long-hauler COVID-19", "ongoing symptomatic COVID-19", post-COVID-19 persistent symptoms" and many more terms have been used to label Long COVID (38,53,55–57). This makes it more difficult for researchers, clinicians and patients to access and collect data and information on the illness consistently. The WHO has recommended using a term that is "unbiased, neutral and non-stigmatizing", which is why Long COVID has prevailed as preferred name by affected people as well as medical staff (53).

In October 2021, the WHO published a clinical case definition of Long COVID by a Delphi consensus, to react to the abundance of heterogenous attempts to define this syndrome. The WHO also called this entity post-COVID-19 condition – or PCC. According to this consensus, "post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time." (58). Many other organisations and institutions have come up with their own definition for Long COVID syndrome. The Center for Disease Control (CDC) described Long COVID as following: "While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for four weeks or even months after recovery from acute illness. Even people who are not hospitalised and who have mild illness can experience persistent or late symptoms." (58,59). The National Institute for Health and Care Excellence (NICE) defined Long COVID as "Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis" (58). In some sources, a distinction is drawn between PACS and post-COVID-19 syndrome – with PACS being persistent symptoms for < 84 days (or four weeks) after infection, representing the direct and indirect effects of SARS-CoV-2 infection and COVID-19. Post-COVID-syndrome is therefore the equivalent to Long COVID, with symptoms lasting for more than 84 days (or at least 12 weeks) (59–61). Other sources define ongoing symptomatic COVID-19 as symptoms persisting for 4-12 weeks after infection, and post-COVID-19 syndrome (or Long COVID) as symptoms persisting for more than 12 weeks (62). The ICD-10 code U09.9 (post COVID-19 condition, unspecified) has been introduced to document Long COVID cases (53).

Unfortunately, all these definitions do not include a clear set of symptoms associated with Long COVID and are therefore criticised for being too loosely set. In response to these inconsistent definitions, the National Academies published a report in order to uniformally define Long COVID – the 2024 NASEM Long COVID Definition. This report describes Long COVID as "an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing

and remitting, or progressive disease state that affects one or more organ systems". It also includes possible examples of manifestation of Long COVID, stating that it can involve almost any organ system (53). The NASEM's definition also includes following characteristics of Long COVID: Long COVID can occur after asymptomatic, mild or severe SARS-CoV-2 infections. It can be continuous after COVID-19 or have a delayed onset of weeks to months after initial infection. It can affect individuals of any age, race, health status, gender, socioeconomic status and geographic origin. In addition to new symptoms, it can also manifest itself as exacerbation of pre-existent illnesses and can range from mild to severe and persist for a few weeks to years. It is a disease to be diagnosed clinically, as there are no biomarkers available. The definition also includes the impact on individuals daily life, as it can impair social life and working ability (53). Compared to previous definitions, NASEM highlights the minimum duration of symptoms for three months, regardless of symptom onset. Symptoms can be consistent, relapsing, remitting or newly occurring after a SARS-CoV-2 infection (53). The three months cutoff was chosen to rule out other possible reasons for the development of symptoms, especially direct consequences of severe illness (not necessarily associated to COVID-19), potentially confounding organ impairment or conditions like post-intensive care syndrome (PICS), mast-cell activation syndrome (MCAS), postural orthostatic tachycardia syndrome (POTS) or ME/CFS (53).

PICS is a severe and long-lasting condition that continues to affect individuals for months or even years after receiving treatment in medical or surgical intensive care units. Prolonged immobility, the administration of large doses of sedatives and neuromuscular blockers, organ dysfunction and septic toxicity can lead to physical impairments like myalgia, muscular weakness and decreased mobility as well as fatigue and chronic myalgia. Furthermore, these factors could lead to psychological symptoms such as anxiety, depression and PTSD, as well as neurological symptoms such as memory loss, attention deficit, polyneuropathy and delirium. In the most severe cases, these symptoms may be permanent (60,63,64). As many COVID-19 patients have been treated on ICUs, naturally, there are many patients with PICS following their COVID-19 disease. After 3-6 months, out of COVID-19 patients treated at ICU about 90% have reported at least one PICS symptom (64). It is characterised by mental and cognitive disorders as well as physical and neurological disabilities. Patients with both conditions, PICS and Long COVID, exist as well. Both syndromes can affect multiple organ systems, and can result in cognitive

impairment and fatigue (53). The diseases may be difficult to distinguish, but there are a few differences. PICS can have non-infectious and infectious triggers (e.g. severe SARS-CoV-2 infections but also pancreatitis etc). Furthermore, cognitive loss in PICS is normally reversible to a certain degree after rehabilitation, while in Long COVID patients, cognitive exercises and training result in clinical worsening. Although fatigue and neuromyopathy are common features of PICS, the post-exertional malaise experienced by Long COVID patients is not typical in PICS (53).

POTS is a type of orthostatic intolerance characterised by hypovolemia and a compensatory increase in cardiac output (56). It can also be triggered by infections, and includes vasomotor and autonomic symptoms like palpitations, hypotonia, lightheadedness and dizziness. POTS is defined as "an increase of heart rate > 30 beats per minute after standing upright for > 30 seconds" without orthostatic hypotension (65,66). Symptoms must be present for at least 3 months for diagnosis (66).

MCAS is a long-term, recurring disorder that affects several organ systems. Its symptoms span a wide range and may include respiratory difficulties such as wheezing, cardiovascular problems like low blood pressure, fainting, near-fainting episodes, or rapid heart rate; and eye and nasal issues such as itching, redness of the eyes, or nasal congestion. Skin manifestations often involve urticaria, swelling (angioedema), or flushing. Digestive symptoms may include nausea, vomiting, diarrhea, or stomach cramps. Additionally, individuals may experience muscle or joint pain, as well as neurological and psychiatric symptoms like headaches, anxiety, difficulty sleeping, or problems with memory and concentration. General symptoms such as fatigue, weakness, or low-grade fever are also common. Diagnosis is often supported by elevated levels of serum tryptase or other relevant biomarkers specific to MCAS (66).

ME/CFS is thought to be caused by viral infections or reactivation, and manifests as "fatigue, post-exertional malaise, unrefreshing sleep, orthostatic intolerance and cognitive impairment", sometimes accompanied by headaches, arthralgia, myalgia and symptoms of general illness like sore throat and tender lymph nodes (53,66,67). It can be triggered by different pathogens like EBV, enteroviruses and dengue viruses and has a worldwide prevalence of 0,3-0,8% (46,51). ME/CFS has also been associated with mitochondrial dysfunction (46). The main symptoms include mental and physical fatigue, post-exertional

malaise, cognitive impairment, orthostatic intolerance and chronic pain (51). In many ways, they resemble symptoms of Long COVID, and Kedor et al have shown, that COVID-19 can trigger a fatigue syndrome that fulfils ME/CFS criteria in a considerable proportion of patients (51). At six months post-infection, approximately one-third of individuals with Long COVID fulfilled the diagnostic criteria for ME/CFS (68). For diagnosing ME/CSF, post-exertional malaise must exceed 14 hours after activity. The reason that patients had Long COVID but did not fulfil the ME/CSF criteria was mostly a shorter duration of post-exertional malaise of under 14 hours. Fatigue and PEM as symptoms were still present, though (51). At least four of the symptoms mentioned above have to be present (66). In contrast to Long COVID, ME/CFS require at least six months of symptoms to fulfil the diagnostic criteria (53,66). Additionally, ME/CFS patients seemed to report more severe flu-like symptoms as secondary symptoms than Long COVID patients (51). No causative therapy has been developed yet for ME/CFS (67).

One semi-systematic, narrative review found five categories of Long COVID to be accurate:

1. Non-severe COVID-19 multi-organ sequelae – organ dysfunction derived from subclinical damage during acute COVID-19; a resulting multi-organ damage may lead to Long COVID symptoms (patients with verified organ damage, through radiological/histological abnormalities)
2. Pulmonary fibrosis sequelae – fibrotic lung changes after ARDS and/or mechanical ventilation during COVID-19
3. ME/CFS – fulfilling the ME/CFS criteria
4. POTS – fulfilling the POTS criteria
5. PICS – after prolonged ICU stay during COVID-19
6. Medical or clinical sequelae – unmasking of underlying illnesses or exacerbation of comorbidities (64).

The german Long COVID guidelines define the syndrome as “symptoms persisting after acute COVID-19 or its therapy, newly developed symptoms after COVID-19 or after SARS-CoV-2 infection than can be understood as its consequence, or the exacerbation of a preexisting disease or illness due to SARS-CoV-2 infection” (69).

Long COVID is increasingly recognised not as a classical infectious disease, but as a post-infectious syndrome and a functional, somatic syndrome (68). It can be included in a range

of post-infectious diseases, summarised by the new term Post-Acute Infectious Syndrome. PAIS can be caused by numerous pathogens, including SARS-CoV-2. It is characterised by overall reduced functional capacity, exercise intolerance, profound fatigue, depressive symptoms, cognitive and sensory deficits, dysautonomia, musculoskeletal symptoms, flu-like manifestations, disruptions of the gut microbiome, and a range of immunologic abnormalities. It is a known consequence of viruses like Ebola, Dengue or Polio, and many others (70).

Goldenberg proposed a different definition in his work, excluding organ-damage directly related to severe COVID-19 from the clinical description of Long COVID, as those consequences can directly be attributed to the initial course of COVID-19. These prolonged symptoms originating in organ damage also correlate with the disease severity. In his definition, Long COVID patients show "no signs of organ damage, have persistent multiple symptoms for a minimum duration of six months, and symptoms must interfere with daily activities" (68).

Due to the great variety in definitions and inclusion criteria, Long COVID is highly underestimated and probably underdiagnosed in certain groups of population (71). The similarities of the different available definitions are symptom onset three months after initial infection and a symptom duration of at least two months (57).

3.2 Pathophysiology of Long COVID

Many different possible mechanisms of developing Long COVID have been postulated. Theories for the causative mechanisms of Long COVID development have focused on persistent viral infection and delayed resolution of the pathogen, chronic inflammation and autoimmunity, reactivation of latent viruses, microclot formation, disruptions of the gastrointestinal barrier and dysbiosis, mast cell activation and specific changes in the CNS. But there are other mechanisms playing a role in the disease's development as well (43,57,68,70).

Viral persistence of SARS-CoV-2 is one of the most suspected pathways, as there is evidence of viral persistence in different tissues of various Long COVID patients months to years after initial SARS-CoV-2 infection (46,49,52,53,72). Viral genome has been found in serum for up to two months, in URT samples for up to three months, in stool samples for up to 126 days and even in the brain tissue (70,72). A reservoir of virus particles or of residues of SARS-CoV-2 could trigger innate immune response by activating host PRRs,

even though the acute infection is over (72). Different types of immune cells, especially NK cells and cytotoxic lymphocytes express features of exhaustion and senescence in Long COVID patients, which point to chronic antigen exposure and persistent immunological response (55,73). T-lymphocyte senescence and activation of monocytes have been associated with increasing Long COVID severity (70). Neutrophil activity appears to remain dysregulated for several months following resolution of the acute SARS-CoV-2 infection (49). Patients also display elevated levels of anti-SARS-CoV-2 immunoglobulins, supporting viral persistence as a pathomechanism (55). Circulating SARS-CoV-2 spike protein subunits have been detected in the plasma of 64% of unvaccinated patients with Long COVID. SARS-CoV-2 mRNA has been detected in 59% of Long COVID patients (38). Many findings point to a subliminal immune response to persistent viral components (38). The bloodstream as well as epithelium, liver, brain, fat and lymphoid tissues may serve as reservoirs for viral persistence for 12 to 15 months following initial infection (52,73).
Viral shedding through the stool of formerly infected patients after recovery has been described in literature, indicating viral persistence in the gastrointestinal tract of COVID-19 patients and potentially leading to long-lasting disruption of the microbiome and subsequent gut dysbiosis (46,73,74). About 1/3 of acute COVID-19 patients show persistent alive virus in gastrointestinal biopsies taken four months after recovery (75).

Intestinal dysbiosis has also been discussed as playing a role in the origins of Long COVID. In addition to changes in the bacterial microbiome, the intestinal virome has also shown significant changes in Long COVID patients (76). Dysbiosis is known to have an effect on immunological processes and especially influence immune response in the lungs through the so-called lung-gut axis, and the CNS through the gut-brain axis. Neurological symptoms like brain fog or fatigue may be caused by changes in the microbiome (56). In one study, 79% of participants with Long COVID had a less diverse intestinal microbiome in favor of pathogenic bacterial variants instead of beneficial ones (74). These changes of intestinal homeostasis may increase gut permeability and fuel inflammatory processes through bacterial and fungal translocation (72,74). Additionally, it has been shown that gut permeability stays dysregulated after COVID-19. This phenomenon also promotes metabolic dysfunction in Long COVID patients, resulting in fatty liver disease, diabetes or IBS (46,52). In the study from Menezes et al, patients with deflected metabolic serum parameters tended to show more severe muscle weakness. They also showed a correlation

between BMI and duration of Long COVID symptoms. Deflected triglycerides, HbA1c and ferritin levels were associated with worse clinical condition in Long COVID patients (77). Reduced serotonin plasma levels have been shown in Long COVID patients, probably caused by reduced tryptophan intake by the intestines (56,68). Tryptophan is a precursor of serotonin and melatonin, and reduced alimentary uptake can be due to high interferon concentrations, inflammatory processes and gut dysbiosis (74). This can contribute to gastrointestinal and neuropsychiatric manifestations of Long COVID, and has been linked to dysregulated hippocampal activity and memory impairment (68). Moreover, dysbiosis and disruption of the intestinal barrier contribute to higher circulating levels of lipopolysaccharides and other toxins originating from the gut, thereby promoting a systemic pro-inflammatory state even further (70).

Chronic inflammatory state could be sustained by postinfectious immunosuppression which often occurs after SIRS as a compensatory mechanism (78). Its technical term is compensatory anti-inflammatory response syndrome, and its purpose is to mitigate the proinflammatory state, prevent maladaptive multi-organ dysfunction, and regulate the restoration of immunologic homeostasis (78). CARS is also the driving cause for the development of PICS, with a persistent state of low-level inflammation, immunosuppression and systemic catabolism, and is hypothesised as Long COVID's cause (52,78). Especially following severe infection and disease, COVID-19 can be succeeded by a sustained immunoparalytic and profibrotic state, Ih underlies an increased vulnerability to secondary infections, reactivations of latent viruses and progressive organ dysfunction, persisting beyond the period of apparent clinical recovery (78). Imaging investigations have revealed chronic inflammation in the lungs, heart, kidneys, liver, pancreas and spleen of patients with severe Long COVID (79). Impaired tissue repair because of modified gene expression could also play a role in Long COVID pathology. Genes coding for fibroblast growth factor 2 and the transforming growth factor beta have been altered in Long COVID patients, further sustaining post-inflammatory tissue damage and hindering regeneration (80).

Other forms of immune dysregulation, such as immunothrombosis, as well as microclot formation have also been suggested (46,52,57). The prothrombotic state observed in COVID-19 is persistent in Long COVID, as the hemostatic and immune system are closely interconnected (46). In both illnesses, microcirculation and the coagulation cascade are

impaired due to dysfunctional endothelial cells (38,46,52). Endothelitis is frequently observed in acute COVID-19 and may persist into the post-COVID condition (67,72). Ongoing endothelial dysfunction in Long COVID is supported by evidence of persistent glycocalyx degradation, elevated levels of circulating endotheliocytes, increased markers of proinflammatory endothelial activation, the presence of microclots and scarcer capillary network density across multiple organs (67,70,79). Microclots have been shown in Long COVID- as well as ME/CFS patients, and are resistant to fibrinolysis (73,79). Microthrombi may disrupt oxygen supply to tissues, which could help explain various forms of tissue-specific dysfunction observed in Long COVID (81). Disorders of the microcirculation are also correlating with fatigue in Long COVID, and tissue hypoxia as well as inflammation is a known cause of small fibre neuropathy (70,73). This could cause various Long COVID symptoms like dysautonomia and neurologic manifestation (73). The vascular approach is supported by significantly higher endothelial biomarkers, which were measured in ME/CFS and Long COVID patients in one study (46). Other results show continuous activation of different types of immune cells in Long COVID patients (46). In a study from Kedor et al, results pointed to low level inflammation, endothelial dysfunction and hypoperfusion as possible pathomechanisms of Long COVID (51).

Additionally to viral persistence, reactivation of latent infections, hence, continuous exposure to the spike protein as superantigen or other antigens could lead to a chronic state of inflammation after initial recovery (52,72). In one study, exaggerated humoral responses were measured in Long COVID patients against SARS-CoV-2 and other herpesviruses (53). Reactivation of EBV, HHV-6, VZV, HSV or CMV during SARS-CoV-2 infection has been observed and discussed as a causing agent of Long COVID (38,46,53,68,70,79). There is growing evidence suggesting that EBV reactivation may contribute to the development of persistent symptoms, especially fatigue and a variety of neurocognitive issues. Previous studies have implicated EBV infection in molecular mimicry with host antigens, the induction of autoreactive immune responses and the aberrant migration and activation of pathogenic B cells (49). Reactivation of latent herpesviruses has been linked to ME/CFS and multiple symptoms of Long COVID (73,79). Gastrointestinal manifestations of post-COVID condition have been associated with an expansion of cytotoxic $CD8^+$ and $CD4^+$ T cell populations specific to SARS-CoV-2 and CMV. Interestingly, this immune activation was observed during the convalescent period, rather than during the acute phase of infection, and coincided with the clinical identification of

Long COVID (49). This suggests a presence of SARS-CoV-2 or other secondary pathogens, triggering a low-level chronic immune response.

Another possible biological pathway is the induction of autoantibodies in potentially genetically predisposed patients during SARS-CoV-2 infection, which has also been shown in multiple studies (38,46,49,52,53,55,67). This process could be triggered by continuous exposure to persisting viral antigens in the body (55). During acute COVID-19, alterations in B-cell function lead to the production of autoantibodies targeting interferons, neutrophils, connective tissue, cyclic citrullinated peptides, and nuclear components. This autoimmune reaction to the pathogen could persist in patients' tissues even after recovery (72,82). Molecular mimicry between components of SARS-CoV-2 and CNS autoantigens and chimeric host-protein formation have been considered as autoimmune mechanisms behind Long COVID (70). Anti-neuronal antibodies have been detected in serum and CSF of critically ill COVID-19 patients showing neurological symptoms (46,50). An increase in new-onset type I diabetes has been recorded post-COVID, suggesting an involvement of beta-cell autoantibodies (46). Studies have also shown that inflammation associated with Long COVID, through the generation of autoantibodies, can initiate autoimmune conditions such as arthritis and systemic lupus erythematosus (SLE) (46). Up to 44% of patients showed elevated ANA titres one year after their initial COVID-19 infection, and were associated with neurocognitive symptoms of Long COVID (49,52). The longterm circulation of other autoantibodies, like antineutrophil antibodies or anticardiolipin antibodies, have also been reported in Long COVID patients (70). In children, multisystem inflammatory syndrome, or MIS-C, is caused by autoimmune processes following severe COVID-19 (53). The autoantigens involved are similar to autoantigens of classical autoimmune diseases (49). Autoantibodies and endothelial dysfunction combined with the prothrombotic state during and after COVID-19 could promote microclot and thrombus formation and cause Long COVID symptoms (46). In contrast to that, other studies found no relevant association between Long COVID development and autoantibody reactivity. Autoantibodies targeting calprotectin, the most frequently identified autoantibody in one study, were associated with a return to baseline health eight months after infection. This suggests that these antibodies may have a protective rather than a pathogenic role (49).

Neurological and psychiatric symptoms of Long COVID are thought to be caused directly by viral invasion of and damage to neuronal organs, or indirectly by disruption of the

brain-blood barrier and inflammatory processes – so-called “neuroinflammation” (46,50). Functional changes in the CNS are a key feature of Long COVID. The role of microglial activation in viral infection-related neuroinflammation is unquestionable in the development of neurodegenerative diseases, accelerated brain ageing and psychiatric diseases such as schizophrenia and major depression (70). Research has identified signaling pathways similar to Alzheimer’s disease in individuals with Long COVID, along with brain hypometabolism (79). In the CSF of Long COVID patients, high numbers of IFN-producing dendritic cells were found, as well as increased numbers of other immune cells, anti-SARS-CoV-2 antibodies crossreacting with neural antigens and elevated cytokine levels (56). Pathomechanisms causing the long duration of neurological symptoms are unclear. Persistent fatigue may be caused by prolonged altered cortisol levels and elevated cytokines (60,68). Dysequilibrium of serotonin metabolism through interaction of the gut-brain axis or viral neuroinvasion have been discussed as possible factors, and reduced levels of serotonin had been shown in IBS and Long COVID patients (59,76). Serotonin is also responsible for pain perception in the GI tract, and dysregulation could be another reason for abdominal pain in IBS and Long COVID (76). Another possible consideration is SARS-CoV-2-mediated altered neuronal signalling in the brainstem and vagus nerve, which could also play a role in dysautonomia reported in Long COVID patients (46,79). In CNS imaging, Long COVID patients showing olfactory and taste disorders had visible alterations in the olfactory bulb. Furthermore, brain areas linked to smell, memory, stress response and fear appeared altered in brain imaging (50). In post-COVID condition, morphologic and functional changes within the limbic system can be found, manifesting clinically as psychosomatic, emotional and cognitive dysfunctions (70). Long COVID patients showed a substantial decrease in grey matter and global brain size, as well as functional changes in brain connectivity and metabolism (65,68). Non-hospitalised individuals with Long COVID demonstrated reduced functional connectivity in temporal and subcortical brain regions compared to control subjects. These disruptions in brain connectivity were associated with cognitive impairment six to nine months after initial SARS-CoV-2 infection, independent of the severity of the acute illness (68). However, no viral RNA was detected in the CSF of Long COVID patients (56).
Recent data has suggested an involvement of mitochondrial dysfunction in the development of neuropsychiatric Long COVID symptoms. Increased levels of total mitochondrial proteins within extracellular vesicles during acute SARS-CoV-2 infection have been identified as predictive risk factor and are associated with neuropsychiatric

manifestations upon disease onset (70,73). Studies examining Long COVID have highlighted several signs of mitochondrial impairment, such as diminished mitochondrial membrane potential and abnormal energy metabolism within mitochondria. Alterations in the processing of fatty acids, alongside ineffective lipid catabolism, have also been observed - patterns commonly associated with reduced physical endurance. These changes are accompanied by imbalances in the redox status, an impaired oxygen utilisation and a reduced exercise capacity (73,79). Mitochondrial dysfunction therefore may induce or aggravate fatigue and muscle weakness (65).

Of course, direct damage to different organs is common as cause of Long COVID as well. Pulmonary fibrosis is a potential sequela in patients after initial COVID-19, which can lead to pulmonary manifestation of Long COVID (78). Besides, tissue damage may be induced by chronic inflammation (83). Epigenetic changes may also play a role in Long COVID development. While data is very heterogenous and clear conclusions cannot be drawn, a systematic review from Shekhar et al showed, that all studies included in their review confirmed epigenetic changes in DNA methylation patterns connected to the immune system, the autonomic nervous system and the cell metabolism (61). In younger patients, evidence for age acceleration and telomer shortening was found, as well as a reduction of the ACE2 expression. However, these results may only be relevant for Long COVID with pulmonary manifestation, and not Long COVID in general (61).

Psychological factors also play a role in the pathophysiology of Long COVID. Factors such as social isolation, loss of loved ones, psychological disorders including anxiety and depression, increased stress, and PTSD can contribute to the onset or worsening of Long COVID symptoms. The emotional burden observed in individuals with Long COVID highlights the interplay between biological and psychosocial factors in the development and persistence of this complex condition (72).

Even though a SARS-CoV-2 infection is obligatory in order to develop Long COVID, sources indicate not one but many different and parallel pathobiological pathways of disease development (53). No definitive biomarker has been identified yet, but researchers have identified various pathological changes in individuals with Long COVID. These identified changes strongly suggest mechanisms including immunological and inflammatory dysregulation, endothelial dysfunction and disturbance of the coagulation

system as pathophysiological Long COVID modifications – but they are not specific enough to explain physiopathology precisely or to identify methods for disease monitoring (84). Substantial gaps remain in our understanding of the clinical manifestations of Long COVID, associated immune signaling pathways, systemic consequences, and long-term pathological profiles. Addressing these gaps will require continued investigation into the underlying immunological mechanisms involved (49).

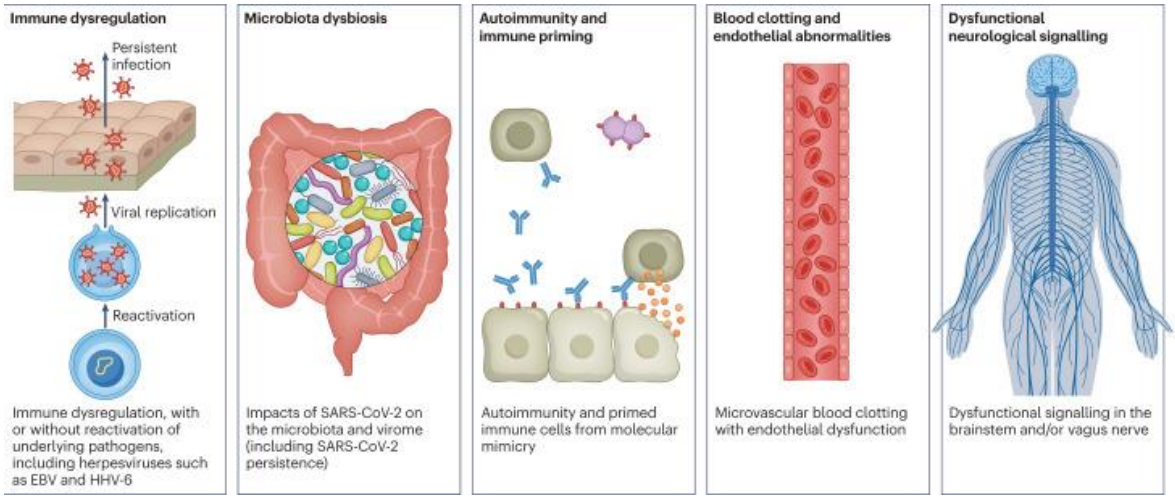

Figure 3 - Assumed pathomechanisms of Long COVID (Davis et al,, 2023, p. 137)

3.3 Epidemiology and Diagnosis

Long COVID can occur in asymptomatic COVID patients as well as in severely ill patients (53). Unfortunately, no definitive biomarker, no laboratory test and no diagnostic criterion exists to specifically confirm or differentiate between Long COVID and other health conditions (53,54). This leads to a high number of unrecorded cases, as patients are likely misdiagnosed (53).

The estimated prevalence for Long COVID varies greatly throughout the literature, ranging from 9 to 35% or even more (39,46,53,85). Between 2020 and 2021, an estimated 17 million people have suffered from Long COVID in the WHO European region (86). The pooled prevalence depending on the continent is spanning from 42,41% in Australia to 49,79% in Asia with a worldwide pooled prevalence of 41,79% (62). Long COVID's incidence is estimated to be 10-35% among non-hospitalised patients (46,52,87). In hospitalised COVID-19 patients, especially severely and critically ill patients, Long COVID prevalence even reaches up to 60%, and incidence between 50% and 85% (46,52,60,87). Other sources found up to 67,5% of non-hospitalised patients to develop Long COVID (38). The RECOVER study found 39% of hospitalised patients and 22% of non-hospitalised patients to develop Long COVID after SARS-CoV-2 infection (85).

Vaccinated individuals experience Long COVID symptoms in 10-12% (52,87). The majority of affected individuals reported experiencing more than one persistent symptom in a 2-6 months follow-up (65). In 2022, Long COVID affected 7,5% of the US population according to the CDC criteria, and between 5-10% of COVID-19 cases in Australia (46,50). The cumulative prevalence varies from source to source, ranging from 9% to 63% in all patients having survived COVID-19 (70). An assumed prevalence of 10% would lead to at least 65 million people worldwide being former or current Long COVID patients (52,53). In spring 2024, the CDC published a survey which revealed that over 17% of US adult citizens have "ever experienced Long COVID", and almost 7% are currently suffering from Long COVID (53). Due to high dark numbers Long COVID is likely to be underestimated as cause of death as well (53). It is believed that in the US alone, by 2023 over 5000 deaths had Long COVID as underlying or contributing cause of death (53).
In low-income and middle-income countries, Long COVID numbers are likely to be underestimated as well. Due to the lack of sufficient infrastructure or sufficient research and therefore reduced testing and reporting of infections, a high burden of Long COVID cases may stay hidden in these populations. As there is also very limited international research data in these countries, the real incidence of post-COVID condition and its consequences stays unknown (87,88).

Possible risk factors for developing Long COVID after SARS-CoV-2 infection are female sex, some chronic illnesses and comorbidities, obesity, negative vaccination status, severity of initial COVID-19 and reinfection (38,52–55,60,65,72). Other sources list depression, low socioeconomic status, personal resilience level, older age, active smoking, need for oxygen supplementation or mechanical ventilation, admission to ICU and hospitalisation as additional risk factors (46,50,54,56,61,65,70–72,85). The comorbidities discovered as possible risk factors were obesity, asthma, COPD, diabetes, depression, immunosuppressive diseases and ischemic heart disease (56,85). Older age apparently influences the severity of post-COVID condition as well as the probability of developing it (70). In some studies, the individual vitamin D level was also associated with different degrees of disease severity (38). A british survey indicated that individuals living in the most socioeconomically deprived areas had, on average, a 46% greater risk of suffering from Long COVID compared to those living in the least deprived areas (56). Other sources state, that younger age is a risk factor for post-COVID condition (61). The association between the severity of COVID-19 and a higher risk for Long COVID has been shown by

multiple studies. Even though mental disorders as a long-term consequence of COVID-19 were also observed among non-hospitalised individuals, the prevalence was the highest in those who required hospitalisation during the acute phase of infection (50). Mood disturbances, psychological stress, and psychosomatic disorders have been linked to an elevated risk of developing Long COVID in some studies (68). Severity of COVID-19 is also a risk factor for developing GI symptoms in Long COVID, with hospitalised patients having a higher risk for GI symptoms than non-hospitalised individuals (74). The presence of GI symptoms during initial COVID-19 is another risk factor for GI symptoms during Long COVID (74). Menezes et al showed, that patients > 45 years of age with more than 15 COVID-19 symptoms at initial disease were 5-6 times more likely to develop severe Long COVID as a consequence (60). The number of symptoms at hospital admission and the time in hospital treatment were both correlating with the number of Long COVID symptoms reported later (53). In contrast, there is data that shows, that 70% of Long COVID patients examined had mild or moderate COVID-19 (61). As already shown, also young and healthy individuals with asymptomatic infection can develop Long COVID, and the severity of COVID-19 does not correlate with the severity of Long COVID (55). The only consistent risk factor in multiple research studies was female sex - women and girls are more likely to develop Long COVID, with an adjusted Odds Ratio of 2,54 of reporting three or more than three Long COVID symptoms approximately eight months after hospital discharge (50,52–54,57,60,72). Approximately 21,2% of SARS-CoV-2 positive women suffer from post-COVID condition, compared to 14,7% of infected men (56). Women aged between 36 and 50 years show the highest percentage of diagnoses, with the highest risk in perimenopausal females, pointing to a possible hormonal factor (46,56). This may be due to immunologic differences during initial infection, as females usually develop less severe courses of COVID-19 than males (56,60,66). Women induce a faster and more effective immune response to initial SARS-CoV-2 infection (56,66). This effectiveness may increase the susceptibility to Long COVID - an immunological pathomechanism is suspected. Women are also more likely to develop autoimmune diseases, as the X-chromosome contains the largest number of immune-related genes. Incomplete inactivation of one X-chromosome has been associated to the development of other autoimmune diseases in the past (56). Additional proposed factors include stronger antibody responses to viral infections, more adverse reactions to vaccines and antiviral medication, and the potential role of X chromosome-linked genes in increasing susceptibility to viral infections and subsequent autoimmune responses. Increased exposure

to the virus in certain professions - such as nursing and teaching - may also contribute to a higher risk of infection. Moreover, women have heightened body awareness and may report illnesses more frequently than males (66). Compared to males, females exhibited more severe symptoms, increased neurologic complications, and greater pain (73). Some symptoms - such as neurological, neuropsychiatric, cardiopulmonary and gastrointestinal - were significantly more likely to be reported by female patients than in males (54). Males with long COVID showed lower estrogen levels than those without the condition, while females with long COVID had reduced testosterone levels compared to their counterparts without long COVID. In both groups, low testosterone levels were strongly associated with immune system dysfunction, inflammation, and clinical illness (73). It is possible, that sex- and immune-related risk factors come together in the female sex, and therefore increase the likelihood of post-COVID condition in women.

Some reports also show a difference in Long COVID prevalence depending on the SARS-CoV-2 strain causing the initial infection. Apparently, earlier SARS-CoV-2 variants harbour a higher risk for developing post-COVID-19 conditions than the Omicron variant (38,43,53). Comparing the incidence of Long COVID in patients infected with the Delta and the Omicron variant, 11% and 5% of patients experienced post-COVID condition, respectively (43,71). An increased risk of Long COVID has also been associated with exposure to disadvantaged environmental conditions, such as air pollution, food insecurity, and neighborhood deprivation (53). In the US, Hispanic and Afro-American individuals have a higher risk of developing Long COVID than White people (53). Even though the syndrome occurs more often in adults and elderly, it can also affect children within the same set of symptoms (82). Among children and adolescents, identified risk factors of Long COVID were older age, female sex, or history of severe disease (either COVID-19, or MIS-C) (53). According to the CDC, almost 80% of individuals suffering from post-COVID conditions experience lifestyle limitations from the disease (53). Younger age (18–29), male sex, non-Hispanic Black people, and the absence of comorbidities were associated with a lower risk of Long COVID (85).

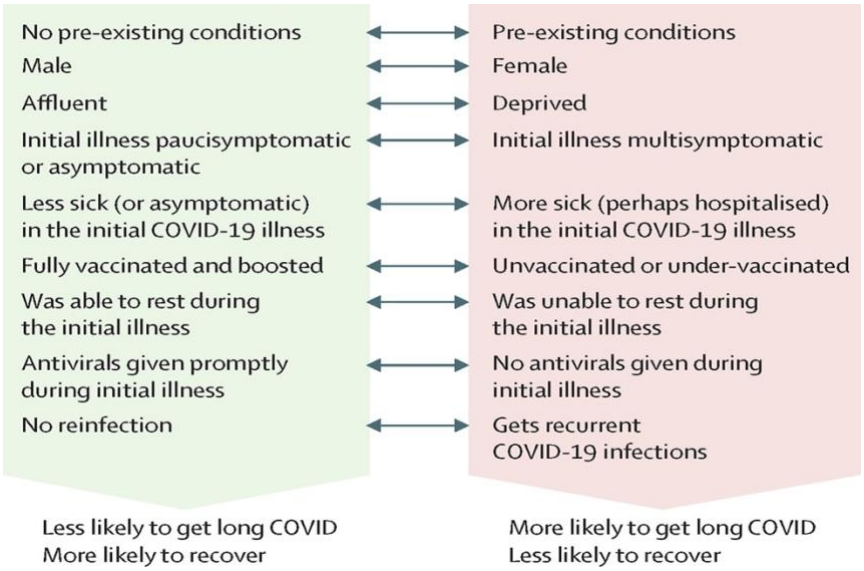

Figure 4 - Summary of risk factors for Long COVID (Greenhalgh et al., 2024, p. 3)

A lot of different biomarkers have been evaluated regarding Long COVID over the past few years. While no distinctive marker could be identified, some could still be helpful in diagnosing Long COVID, especially when considering them as part of the big picture. Generally, Long COVID patients had higher serum levels of proinflammatory substances, cytokines and acute phase proteins than healthy individuals (54–56). On the other hand, innate cellular marker levels did not show significant correlation to different Long COVID symptoms (84). If we consider chronic low-grade inflammation to be one of Long COVID's main triggers, the measurement of CRP levels is insufficient to confirm this allostatic state. Other systemic inflammatory markers and markers of endotheliosis are necessary. The criteria for low-grade inflammation are CRP levels of 3-10 mg/L, heightened fibrinogen and an increased neutrophil/lymphocyte ratio. These criteria are all fulfilled by Long COVID patients regardless of the initial COVID-19 severity (70). In one of the first studies concerning Long COVID, researchers found IL-8 to be elevated in 37-48% of Long COVID patients (51). Elevated SARS-CoV-2–specific immunoglobulins have been identified in individuals with Long COVID, and elevated IgG titers were correlated with an increased risk of developing post-acute COVID-19 syndrome. After 12 months, IgG immunoglobulins decreased again – instead, ANAs were detected and associated with Long COVID (55,56). Elevated ANAs were found in eight out of 42 patients. They also found vitamin D deficiencies in 11-22% of patients, and decreased levels of folic acid in 19%. ACE1 was also reduced in 31% of Long COVID patients (51).

In a study by Klein et al, no correlation between autoantibody production and Long COVID was detected (83). Examining the role of the complement system, elevated levels of complement C6, C7 and complement factor-1 were revealed (55). Large amyloid deposits and hyperactivated platelets forming microclots have been identified in the plasma of Long COVID patients, containing elevated levels of coagulation-related proteins such as plasminogen, fibrinogen α and β chains, α2AP, vWF and the coagulation factor XIII (38,55). Klein et al found a significant association between plasma levels of non-conventional monocytes and an elevated MHC class II expression in Long COVID patients. They also discovered that cortisol levels seemed to be significantly lower in Long COVID patients than in healthy control groups. Decreased cortisol levels did not trigger rising ACTH-levels, which indicates a disturbance of the hypothalamic-pituitary axis (56,70,83). Lowered cortisol levels even turned out to be the most significant predictor of Long COVID within the biomarkers investigated in this study (68,70). Patients who were going to report persistent pulmonary symptoms displayed low serum cortisol levels (81). Supporting the hypothesis of viral reactivation in Long COVID, affected individuals showed elevated IgG reactivity against EBV and VZV without an active infection (56,83). In a systematic review of many investigated biomarkers, IL-6, CRP, TNF-alpha, IL-17, IL-4, ferritin and CCL-2 were upregulated and may support a Long COVID diagnosis, if already suspected (54). Increased IFN-γ levels were also detected in COVID-19 patients initially, as well as in Long COVID patients following initial infection (55). Elevated levels of TGF-β have been detected in patients during COVID-19 as well as 11 months after recovery (55,78). GM-CSF and CCL4 levels were lowered in COVID-19 patients, who later went on to develop Long COVID (55).

Furthermore, exhausted lymphocyte populations were identified in Long COVID patients, along with an increase in different types of inflammatory monocytes (55,70,72,83). Klein et al also concluded, that the T-cell function was altered, as CD4+ cells produced significantly higher amounts of interleukins after stimulation compared to healthy controls. Specific subsets of CD4+ and CD8+ T-cells were increased, resulting in significantly changed circulating immune cell populations, again suggesting inflammatory processes (72,83). Another source found central CD4+ memory T-cells to be reduced, while activated B-lymphocytes seemed to be increased (70). Similarly, a separate study reported that individuals with Long COVID exhibited decreased numbers of $CD4^+$ and $CD8^+$ effector memory T-cells, alongside elevated expression of PD-1 on central memory T cells (49). Total CD8+ T-cell count was increased, while naïve CD8+ T-cells were decreased in

Long COVID patients. This suggests chronic T-cell activation and an ongoing antiviral immune response (55).

Researchers have tried to stratify biomarkers and to categorise patients into groups according to their biomarker profiles. TNF-alpha was strongly associated with cough and fatigue as main Long COVID symptoms reported (84). Elevated CRP was associated with multiple, pulmonary and neurological symptoms (54). Patients who exhibited higher levels of VEGF and NFL in combination with decreased hemoglobin experienced worse Long COVID symptoms (54). In Long COVID with neurological manifestation, NFL and glial fibrillary acidic protein were elevated in affected patients, indicating tangible neuronal damage and astrocytic activation or dysfunction (46,54,55). Higher levels of SARS-CoV-2 containing exosomes were also associated with neurological Long COVID (55). Patients with deflected neurological biomarkers had worse headaches and stronger neuropathic pain (54). Interestingly, higher levels of markers of fungal and bacterial translocation like ß-glucan, lipopolysaccharide binding protein and zonulin were also detected among Long COVID patients (55,73,79). These two markers were linked to neurological symptoms like vision impairment, pain, neuropathy and sleeping disorders. This would support the gut dysbiosis in Long COVID patients as one possible pathomechanism of the disease (55). Other groups found IL-6 and TNF-alpha to be associated with neurological manifestation, and La/SS-B antibodies to be specific for gastrointestinal Long COVID symptoms (84). Individuals who later developed neurological symptoms showed increased levels of proteins linked to circadian regulation (81). Additionally, persistently high CMV-specific CD8+ cells and ß-glucan levels were correlated with GI manifestation (55,81). Fecal shedding of SARS-CoV-2 was also shown to be correlated with GI symptoms (76). Biomarkers, specific for fatigue as leading symptom, were related to vascular dysfunction and endothelial damage, but also EBV reactivation. These include Endothelin-1, AT-2 and endothelial peripheral dysfunction, as well as EBV viremia in the acute phase of disease (55,81).

For Long COVID with pulmonary manifestation, transforming growth factor beta (TGF-β), a profibrotic and anti-inflammatory cytokine, showed potential as biomarker (53). In another study, dysregulated subsets of CD4+ and CD8+ T-cells were correlated to pulmonary manifestation of Long COVID, namely exhausted and highly cytotoxic T-cell populations (55,84). IL-6, CRP and TGF-β were shown to correlate with risk of pulmonary fibrosis as severe complication after SARS-CoV-2 infection (54). Elevated vascular

biomarkers like VEGF, vWF antigen and vWF propeptide, among others, were also associated with multiple Long COVID symptoms (54).
One research group found angiopoietin-1 and P-selectin to be accurately identifying Long COVID patients (79,84). Menezes et al linked higher ferritin levels in Long COVID patients with shorter duration of symptoms of up to 90 days, while patients with lower ferritin levels presented clinically ill for more than one year (77). Two other studies found IFN-γ to be decreased in Long COVID patients and suggested it as Long COVID biomarker (84). Fecal multi-biome profiling may also hold potential as a prognostic tool for predicting the development of Long COVID (76). No metabolic blood biomarker could sufficiently be linked to Long COVID (84). In a comprehensive assessment and meta-analysis, Long COVID patients were found to have higher levels or CRP, D-dimer, LDH, IL-6 and leukocytosis (52,72). IL-6 was generally the most frequently dysregulated biomarker in Long COVID patients (57,84). In a systematic review of Lai et al, CRP, IL-6 and TNF-α have the highest potential for identifying Long COVID patients (54). Even though CRP levels normally subside after three days following infection, persistently increased CRP was reported in Long COVID patients for up to seven months after initial SARS-CoV-2 infection (55,84). VEGF also showed potential as a Long COVID diagnostic biomarker. Still, it is unlikely that one single deflected biomarker like CRP or VEGF can sufficiently be used for a definitive diagnose (84). One research group found biomarkers in BAL samples to be dysregulated more significantly than blood biomarkers (84), indicating a possibly wrong approach to Long COVID diagnosis. In summary, out of 25 routine laboratory markers, none showed the potential as clinically useful biomarkers for post-COVID condition (85).

As many clinical signs of Long COVID are overlapping with other health conditions, clinicians may be restrictive with diagnosing this disease. Some biomarkers could have predictive value when measured during the acute phase of COVID-19, mainly composed of chemokines, cytokines and VEGF. Most commonly, IL-2, IL-4, IL-6, IL-10, IL-17, IFN-γ and few CCLs were upregulated in COVID-19 patients, correlating with Long COVID risk (55). As there is no definitive biomarker or symptom, that is pathognomonic for the syndrome, they may not be confident, that they had eliminated enough differential diagnoses (53,57). Because of that, the NASEM Definition has included diseases like POTS or ME/CFS into their definition, as these conditions may develop from Long COVID and similar clinical presentation should not hinder patients receiving the right

diagnosis (53). Especially because there is evidence that the resembling clinical presentation may root in a common pathophysiological pathway (53).
Long COVID is still an exclusive diagnosis, in which other possible somatic and psychologic diseases have to be ruled out before making the final diagnosis (e.g. postinfectious mononucleosis) (69). Even asymptomatic exposure to SARS-CoV-2 may trigger a response capable of contributing to the development of Long COVID, which is why PCR-positivity is not considered necessary for diagnosis anymore (71). A physical examination in suspected Long COVID patients should include vital and baseline laboratory parameters. These should include a complete blood count, serum electrolytes, kidney function, blood glucose level, HbA1c, thyroid function and an electrocardiogram (57). Neuropsychiatric manifestation should be evaluated by psychological assessment, cognitive impairment screening and sleep quality assessment (57). In multimorbid, old patients, nursing staff should pay special attention to so-called ‘soft signs’, like reduced appetite or confusion to recognise the diagnosis as soon as possible. Comprehensive post-acute assessments for patients with post-COVID condition should be carried out in long-term care facilities 4–6 weeks after symptom onset or the patient's return from a hospital setting (89). Subjective dyspnea should be assessed with the 6-minute walking test. Patients with cardiac comorbidities should be evaluated regularly including troponins, echocardiography, electrocardiogram and chest x-ray (57). For detecting cardiovascular or thrombotic manifestations, MRI scans can be used, if available. Interestingly, dogs are capable of detecting Long COVID patients through the smell of their sweat (79). The lack of uniformity in the international clinical definitions and diagnostic criteria for Long COVID makes it difficult to establish a gold standard for diagnosis. This hinders the development of consistent care protocols and treatment strategies for affected individuals. Because of that, diagnosis of Long COVID remains highly subjective due to considerable variability in symptom onset, the absence of pathognomonic clinical features, concurrent reactivation of other conditions, the presence and exacerbation of pre-existing comorbidities and diseases, as well as the heterogeneous and multifaceted nature of its manifestations (71).

3.4 Symptoms and clinical appearance

The 2024 NASEM Long COVID Definition includes possible symptoms in their definition, but these are not exclusively necessary for diagnosis. It states, that “patients can present with shortness of breath, cough, persistent fatigue, post-exertional malaise,

difficulty concentrating, memory changes, recurring headaches, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation and diarrhea" (53). Nonspecific symptoms also include arthralgia, generalised or chronic pain, fever or chills, sweating, weight loss, hearing impairment or tinnitus, red eyes, edema, renal failure and sore throat (60). In addition to nonspecific symptoms, they can present with diagnosable conditions as part of Long COVID, like "interstitial lung disease, hypoxemia, cardiovascular disease, arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome, mast cell activation syndrome, fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, autoimmune disorders such as lupus, rheumatoid arthritis and Sjogren's syndrome" (53). The most common symptoms reported were post-exertional malaise (87%), fatigue (up to 91,6%), brain fog (64%), dizziness / lightheadedness (62%), headaches (20-55%), sleep disturbances (20-50%), dyspnea (43,3%), arthralgia or myalgia (27,3%-60%), chest pain (21,7%), GI symptoms (59%) and palpitations (57%) (39,52,53,55,59,60,65,68,71,85). Other sources list fatigue, tiredness, fever, chills, generalised pain, impaired physical and cognitive functions, anxiety, depression, sleep disorders, diarrhea, new-onset diabetes, stomach pain, loss of taste and/or smell, rhinorrhea, joint or muscle pain, neuropathy, rashes, hair loss, sexual dysfunction, palpitations, chest pain, cough, sore throat, sputum production, dyspnea, ear pain, tinnitus, peripheral neuropathy and headaches as examples of clinical presentation (38,46,50–52,54,55,59,60,64,66,68,90). In younger adults, fatigue (95%), cardiological, pulmonological and neurological symptoms are the most common (59,60). In children and adolescents, Long COVID can also manifest in almost any organ system (85).

All symptoms go hand in hand with a severely impaired life quality (67). Many patients do not show signs of morphologic organ damage which makes this syndrome even harder to describe and diagnose (68). A change in symptoms depending on SARS-CoV-2 strain was also observed, with an increase in myalgia, cognitive difficulties and anxiety, alongside a decline in symptoms like anosmia and dysgeusia during the Alpha wave (81).

Symptom duration is very variable during Long COVID. They can be newly occurring, relapsing, intermittent and varying in severity and organ manifestation (71,75). Different studies show proportions of up to 85,9% experiencing symptom relapses during one month after acute infection. These relapses can be triggered by mental and physical exertion, as well as emotional stress or menstruation (55,91). Other sources show that some symptoms

tend to worsen over time - especially neurocognitive symptoms - while others resolve within a few months' time after acute COVID-19 (65). Neurological symptom onset is commonly delayed, and correlates with younger age (79). In addition to that, new symptoms that were not present during acute COVID-19, like anosmia, post-exertional malaise and cognitive disorders, often occur primarily months after the initial SARS-CoV-2 infection (53). In data from the UK National Statistics Office, 41% of Long COVID patients still experienced symptoms one year after initial SARS-CoV-2 infection (56). Other sources reported persistent symptoms in 40% of individuals after two years post infection (72). Respiratory and gastrointestinal symptoms tend to resolve within a few weeks (59,65). Symptoms reported more commonly through 6-9 months after infection were mostly cough, ageusia, anosmia or headaches. Fatigue, sleeping disorders, dyspnea and myalgia were more likely to be reported after 12 or more months postinfection (53). Generally, symptoms can persist for multiple years after SARS-CoV-2 infection and can range from mild to severe (53). A summarisation of Long COVID's most common symptoms can be seen below in Figure 4.

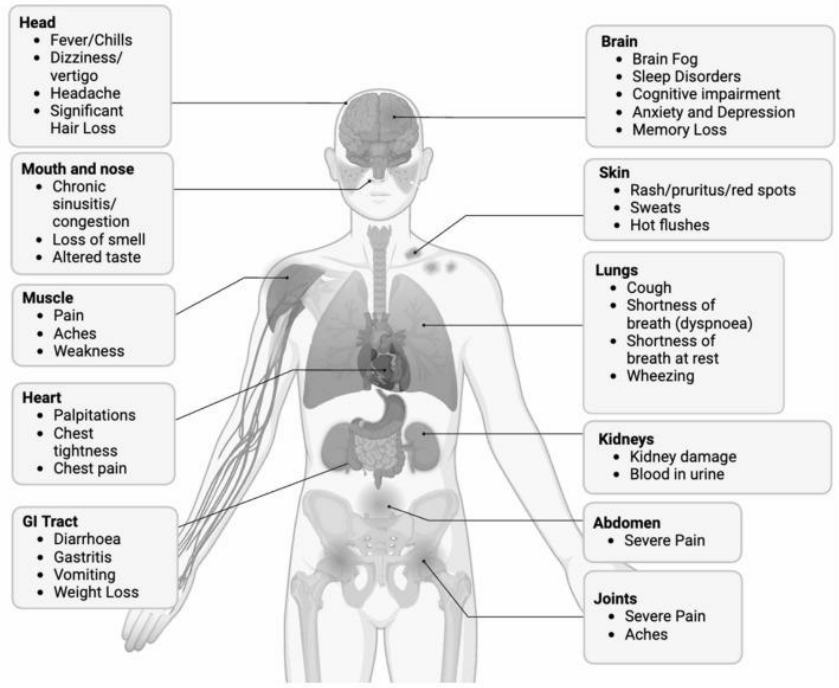

Figure 5 - Most common Long COVID symptoms (Donald et al., 2024, p. 17)

Some research groups have tried to categorise Long COVID by clinical characteristics and symptom groups into pulmonary, GI, neurological, musculoskeletal, cardiovascular and psychiatric. The RECOVER study categorised patients into four clusters, depending on

clinical presentation: Cluster 1 only had changes in smell and taste, cluster 2 had post-exertional malaise and fatigue, cluster 3 had brain fog and cognitive impairment or fatigue and post-exertional malaise, and cluster 4 patients suffered from multiple symptoms combined of the clusters above plus gastrointestinal or cardiac symptoms (85). Yong and Liu categorised Long COVID as a syndrome with the following subtypes: non-severe COVID-19 multi-organ sequelae; pulmonary fibrosis sequelae; ME/CFS; POTS; PICS and medical or clinical sequelae (64).

Cardiovascular and pulmonary symptoms are relatively common in Long COVID. Cardiac complications and elevated risk of disease after COVID-19 even affects patients who were not hospitalised during their initial infection (52). Pulmonary symptoms, especially dyspnea, are among the most frequent symptoms reported in hospitalized and non-hospitalised patient groups (59). Pulmonary symptoms include persistent cough, dyspnea, sleep apnea and chest pain (56,60,70). They can result from persisting direct organ damage following SARS-CoV-2 infection, like interstitial lung disease and other lung pathologies, local inflammation and immunologic dysregulation, thromboembolic diseases, platelet pathologies or endothelial dysfunction causing hypoxemia with an increased demand in supplemental oxygen, arrhythmia or tachycardia – or the onset of these symptoms without evident pathological correlate (53,65). In children, 69,8% of post-COVID sufferers had a residual cough as pulmonary symptom (59). Approximately 5–8% of COVID-19 patients develop acute respiratory distress syndrome (ARDS). During the last fibrotic phase of ARDS, IL-1β, TNF, and IL-6 are released, accompanied by neutrophil infiltration and disruption of the endothelial–epithelial barrier. These processes may lead to chronic fibrotic remodeling, lung fibrosis and pulmonary hypertension, resulting in prolonged breathlessness, chronic cough and supplemental oxygen demand and other pulmonary symptoms of Long COVID (56,60). Dyspnea is associated with worse sleeping quality, mood disturbances and diminished life quality of 12 months after COVID-19 (57). Many imaging studies have consistently identified pulmonary abnormalities in individuals with Long COVID. COVID-19 and SARS-CoV-2 infections enhance processes like coronary arteriosclerosis and cardiac fibrosis, which can cause cardiac dysfunction in Long COVID. After COVID-19, patients have an elevated risk of heart failure, myocardial infarction and cardiogenic shock. Cardiological symptoms described in Long COVID include arrhythmia, myocarditis, palpitations, tachycardia, chest pain and arterial hypertension (65). Cardiological symptoms in Long COVID can also have many different causes, ranging

from direct viral invasion of heart tissue to local inflammation, molecular mimicry with cardiac autoantigens, sarcomere disruption and fibrotic changes in reaction to immune responses (65,91).

Among COVID-19 patients, coagulopathy is a thoroughly described manifestation. After acute infection, the prothrombotic state persists and may result in thromboembolic events such as cerebrovascular accidents, myocardial infarction, or pulmonary embolism. This can lead to persistent impairments in various body regions, depending on site of the event (78). Fibrinolysis is impaired in Long COVID patients, and antiphospholipid-antibodies can further enhance the coagulation. The coagulopathy linked to acute and Long COVID has shown certain similarities with the thrombotic patterns seen in antiphospholipid syndrome (81). Pulmonary embolisms are the most commonly reported hematological consequence in patients already recovered from COVID-19 (52). HRs are 3,16 for pulmonary embolisms, 1,52 for strokes and 2,55 for deep vein thrombosis after acute COVID-19 (81).

Long COVID can cause a variety of neurological and psychiatric symptoms. Approximately 80% of hospitalised patients experience neurological manifestations of Long COVID (56). Neurological and cognitive symptoms usually stay present for up to six months or longer after recovery, and may worsen over time (52,59). Following 12 months after infection, patients have an elevated risk of epilepsy, seizures, ischemic stroke, cognitive dysfunction and sleep disorders compared to healthy controls (52,53). The neurological complications faced by Long COVID patients range from “cerebrovascular disorders, peripheral nerve disorders, movement disorders and Guillain-Barré syndrome to encephalitis or encephalopathy and transverse myelitis” (56). About 60% of COVID-19 patients continue to experience neurological symptoms related to the break-down of the blood-brain barrier and worse longtime outcomes (50). The RECOVER study showed, that brain fog (64%), dizziness (62%) and motoric dysfunction (15%) were generally among the most common Long COVID symptoms still present after six months post infection (59). Anosmia and dysgeusia are amongst the most common symptoms appearing in children with Long COVID (70). Following acute COVID-19, encephalopathies, Guillain-Barré-syndrome, ischemic strokes, cranial nerve damage, polyneuropathy and plexopathies can occur (69). Headaches and body aches occur in 44% and 19% (69). The neuropsychiatric manifestations of Long COVID encompass a range of symptoms,

including fatigue, cognitive impairment or brain fog, headache, generalised pain, sleep disturbances, dizziness, balance problems, paresthesia and tingling sensation in the extremities, altered olfaction and gustation, as well as mood disorders such as dysphoria and depression, sensitivity to light or noise, anxiety, obsessive-compulsive disorder, attention disorder and paranoia (50,52,56,60,69,79). Persistent fatigue, brain fog (especially memory loss and cognitive issues), headache, anosmia and dysgeusia after SARS-CoV-2 infection are the most commonly reported neurological symptoms (92). Cognitive symptoms associated with Long COVID appear to be relatively consistent. Prevalence of psychiatric manifestations are 40% sleep disturbances, 60% fatigue, 42% depression, 42% anxiety disorder, 34% PTSD, 20% stress symptoms and 20% obsessive-compulsive disorder (69). Brain fog is another term coined by Long COVID patients, describing "a certain fuzziness of thinking" or cognitive impairment, more specifically being deficits in concentration, attention, verbal memory, psychomotor skills, cognitive processing speed, and executive functioning (52,70). Greater deficits are observed in individuals with severe acute COVID-19, former inpatient care, and history of depressive symptoms and sleep difficulties (50). Other sources report a higher incidence of brain fog in women with preexisting mental health conditions and women with mild initial infection (68). Brain fog affects approximately 66% of Long COVID patients and is associated with psychiatric post-COVID symptoms (70). In children, the incidence of brain fog ranges between 2-44% (70). Fatigue, on the other hand, could be categorised into physical and cognitive fatigue. Some sources even subdivide dimensions of fatigue further, including mental fatigue and emotional fatigue as separate entities (86). Its definitions vary greatly through the literature, but to summarise it, it describes a state of excessive tiredness and exhaustion, physical and/or mental, and muscular weakness, making everyday tasks and activities unproportionally more effortful for affected individuals (86). The prevalence of fatigue even increased throughout a 2-year-period in non-hospitalised patients, from 34% to 53% (68). Affected patients are mostly women, and 88% or patients have post-exertional malaise as well (69). Cognitive impairment in Long COVID is not necessarily associated with mental health status or with hospitalisation status during COVID-19 (79). Sleep disorders have been reported in 45–56% of individuals with Long COVID. Symptoms include insomnia, difficulties falling asleep, sleepiness during daytime and frequent awakenings (68). Post-exertional malaise, which is also among the most frequently reported neurological Long COVID symptoms, is characterised by intolerance to mental or physical activity. When patients exert themselves mentally or physically, this

leads to an aggravation of symptoms for a minimum of 14 hours per definition (51). It affects almost half of Long COVID patients and can be triggered by exercise or by activities of daily life like household chores, personal hygiene, social interactions etc., which makes it very debilitating for patients, as it severely impaires everday life quality (91). Fatigue and post-exertional malaise cannot be clearly separated from each other, as they often overlap, and fatigue is one of the most reported symptoms to be aggravated after exertion in the sense of post-exertional malaise (86). Fatigue and post-exertional malaise are also among the key symptoms of ME/CFS. According to the literature, up to 40% of all Long COVID patients meet the criteria for ME/CFS. Symptoms listed above are also most frequently reported to require reduced working hours – with 22% even unable to work entirely (51). Psychiatric consequences of COVID-19 include anxiety disorder and psychotic disorder (52).
Persistent headaches among individuals with post-COVID condition can manifest as tension-type or migraine headaches and rank among the five most frequently reported symptoms in Long COVID (68). Altered taste and smell in individuals with Long COVID may stem from direct invasion of olfactory cells, local inflammation or a disrupted gustatory threshold (65). Changes in smelling ability have a severe effect on life quality of patients. People with parosmia frequently lose weight (as a result of reduced enjoyment of eating) and develop depressive symptoms (57).

Autonomous dysregulation is listed as a Long COVID symptom as well, with POTS as the most common manifestation. These symptoms do occur more frequently in females and in younger patients (51,53). Around 80% of patients with post-COVID condition meet the criteria for POTS, supported by nerve biopsy findings indicating small fiber neuropathy (56,68,73). Other sources estimate that 2-14% of COVID-10 survivors develop POTS 6-8 months after the infection (91). POTS can be diagnosed by tilt-table testing (57). Postural hypotension can also be a manifestation of autonomous dysfunction in Long COVID, characterised by a drop of systolic blood pressure > 20 mmHg after standing for more than three minutes (65). Dysautonomia can affect almost any body region and can also be responsible for GI symptoms. It can manifest as nausea, abdominal pain, constipation or diarrhea in the GI tract (74). Dysautonomia can also be responsible for changes in smell or taste, hypoxia or headaches in Long COVID patients (57).

Renal injury was also reported as part of Long COVID as disease entity. Considering a six month follow-up, 35% of former COVID-19 patients had renal dysfunction (52). There are reports ranging from acute renal injury to end-stage kidney disease developing after recovery from COVID-19 (52). Persistence of the SARS-CoV-2 N-protein within the renal tubular epithelium has been documented in individuals recovered from COVID-19. Thus, renal damage occurs through direct viral damage, and acute kidney injury developed during COVID-19 may lead to chronic kidney disease in Long COVID (70).

There is evidence of Long COVID causing "musculoskeletal, immunological, systemic and rheumatic diseases like rheumatoid arthritis, lupus, diabetes and Sjogren's syndrome (53). Some studies suggest a connection between Long COVID and MCAS, fibromyalgia and even Ehlers-Danlos syndrome (53). In some Long COVID patients, clinical presentation resembles MCAS, and activated serum tryptases were significantly elevated compared to asymptomatic or healthy individuals (49,73). Arthralgia represents a common clinical feature of Long COVID, even though no evidence of local inflammation like arthritis or myositis can be found (70). Myalgia and muscle weakness is a frequent symptom of acute COVID-19, and can persist for over a year after infection (70). In the study from Kedor et al, muscle fatigue was tested by assessing hand grip strength, and most Long COVID patients were below cut-off values (51). Results point to endothelial dysfunction, low level inflammation and hypoperfusion as causes of muscle fatigue (51). Myalgia and arthralgia can be found in 40-60% of Long COVID patients (68). The most commonly reported sites of pain included the neck, lower extremities, and the head. Structural alterations in muscle tissue, indicative of exercise-induced myopathy, have been observed in patients with severe Long COVID. Ten percent of individuals with persistent symptoms following SARS-CoV-2 infection met the diagnostic criteria for a central sensitisation disorder, also referred to as nociplastic pain (68). Manifestations of the integument have been heavily reported as well, with hair loss and dermatological efflorescences like rashes as most frequent symptoms (52,60). Rhagades and exsiccosis of the hands in the form of toxic hand eczema have been reported (69). Telogen effluvium has been reported by more or less than 20% of Long COVID patients in a Chinese study (52). Hair loss could be triggered by elevated IL-6 levels in Long COVID patients, as the cytokine suppresses matrix cell proliferation within hair follicles (60). It was shown to be more common in patients infected with the Delta variant of SARS-CoV-2 (91). Diabetes mellitus type I has also been shown to be caused by immunological processes following COVID-19. Autoantibodies

attacking pancreatic cells or peripheral insulin sensitivity decrease may be the mechanism behind this (52). Direct SARS-CoV-2 infection of pancreatic tissue has also been shown, and could be an alternative pathomechanism in post-COVID diabetes development (73). In the eye, Long COVID can cause retinal thrombosis or hemorrhage, cotton wool spots and microcirculatory disorder. Changed pupillary reflexes and corneal small fibre loss have also been shown (79).

GI symptoms in Long COVID are also common, as COVID-19 can manifest in the GI tract as well. Persistent GI symptoms have a prevalence of 10-25%, depending on literature (74). The likelihood of developing GI symptoms increases with greater severity of COVID-19, GI involvement during the acute disease and psychological distress occurring before or after infection (74). Life quality is significantly lower in Long COVID patients displaying GI symptoms than for patients without GI manifestation (74). The most common symptoms are nausea and vomiting (60). Other manifestations can be abdominal pain, diarrhea, GERD, constipation and loss of appetite (56,74,76). Patients may experience persistent GI symptoms, including dyspepsia, chronic bowel dysfunction, and IBS 6 months post recovery (52). A great proportion of patients meet the criteria for the post infection irritable bowel syndrome, which is characterised by abdominal discomfort, pain and changed bowel habits. IBS patients also have a lower pain threshold to bowel distension called “visceral hypersensitivity” (74). Most of the GI symptoms experienced during Long COVID can be categorised as functional GI diseases (68,76). Intestinal dysbiosis and the subsequent disturbance of the gut-brain axis may be one of the reasons for GI Long COVID symptoms, lasting up to six months post infection (52,76). Multiple severe cases of post-COVID-19 cholangiopathy have been reported, indicating a potential risk for long-term hepatic complications (70). The hazard ratio of developing cholangitis in the post-COVID period is 2,02 (74).

Long COVID can also lead to exacerbations of pre-existing illnesses. An elevated risk of diabetic ketoacidosis has been observed in individuals following SARS-CoV-2 infection. Another study found worsening of symptoms in 68% of patients with preexisting POTS (53). Pre-existing headaches are associated with prevalence and severity of headaches after COVID-19 infection (68). Long COVID also affects the menstrual cycle of female patients, possibly changing menstrual symptoms and cycle length (63). Relapses were

shown to be triggered by menstruation (79). Long COVID can cause exacerbations of cardiological, pulmonary, neurological, mental, GI and vascular diseases (64). Concerning mental health in Long COVID patients, there is heterogenous data. In the study from Kedor et al, mental health was not relevantly impaired in most Long COVID patients (51). Other sources found increased rates of PTSD in Long COVID patients formerly treated in ICUs (50). In other sources, prevalence of depression and anxiety in Long COVID were reported at 23% and the risk of major depression and anxiety was 3,4 times higher than in healthy individuals (68). In a systematic review and meta-analysis, the pooled prevalence of depression and anxiety was 23%. The pooled prevalence of sleeping disorder was 45% (93). The specific ways in which post-COVID condition leads to the onset of depression and anxiety are still not fully understood yet. One hypothesis is the increased amount of stress that affected individuals experience during the course of the disease – physically and mentally. Further, unemployment, economic hardship, and reduced social interaction can play a role. Another hypothesis are the effects of immunoregulatory dysfunctions on the brain (93).

3.5 Treatment options for Long COVID

At present, there is no universally accepted treatment protocol for Long COVID throughout clinical practice (88). Evidence suggests vaccination as protective factor against Long COVID. Many authors found that vaccination reliably decreases the risk of Long COVID, but it does not fully prevent it (56,57,70,73,94). Twice vaccinated individuals have a 40-60% lower prevalence of Long COVID and a lower risk of fatigue and pulmonary symptoms than unvaccinated individuals (56,57). Researchers have also found that each following vaccine dose reduces the risk of Long COVID additionally (56). However, the results indicate that COVID-19 vaccination after SARS-CoV-2 breakthrough infection only provides partial protection against post-COVID condition (69). Only one administered vaccination was not significantly associated with lower Long COVID incidence (94). Among individuals with existing long COVID, responses to vaccination are variable. Around 16-20% report symptom improvement, 20-21.4% experience symptom worsening, and the rest notice no significant difference after receiving the vaccine (79,94). Symptomatic worsening following COVID-19 vaccinations were mostly common vaccine side effects like fever or chills. If specific Long COVID symptoms worsened, mainly brain fog or anosmia, the majority resolved within 7 days after vaccination. Therefore, symptom exacerbations after COVID-19 vaccine are probably only temporary reactions and do not

aggravate the post-COVID condition (94). Still, it is not clear which effect vaccination has on already diagnosed patients (72). Some patients develop PCVS after COVID-19 vaccination, which causes similar symptoms while the pathomechanisms stay unclear (95).

An early start of antiviral medication during acute COVID-19 also shows significantly protective effects against developing Long COVID (87). These two protective factors are indirect evidence, that high viral replication and viral load during SARS-CoV-2 infection play a role in Long COVID pathomechanisms (73).
Proposed therapeutic options for long COVID include apheresis, antivirals like nirmatrelvir/ritonavir (Paxlovid), and antihistamines like loratadine, fexofenadine, and famotidine. Anticoagulants like apixaban and antiplatelet agents such as aspirin and clopidogrel have also been suggested. In addition, antithrombotic agents including nattokinase, serrapeptase, lumbrokinase, and bromelain have been identified as potential options of intervention (57).
Unfortunately, the STOP-PASC trial showed no beneficial effect of nirmatrelvir/ritonavir, taken in by Long COVID patients for 15 days. Another clinical trial (the PAX LC trial) is currently underway, examining the effect of Paxlovid-intake in a broader Long COVID population (74,96). Hospitalised COVID-19 patients should undergo a checkup concerning possible long-term effects 8-12 weeks after (40).
Pirfenidon, an antifibrotic drug targeting TGF-β, has positively affected post-COVID-19 pulmonary fibrosis development in one trial (54). Still, for pulmonary impairment, pulmonary rehabilitation is the most recommended therapeutical option (64). Interestingly, metformin was associated with a 41% reduction in the incidence of Long COVID compared to placebo drugs, due to its anti-inflammatory effects (56,67). Apparently, it also shows antiviral effects and successfully reduced the viral load in a follow-up analysis (73). Furthermore, there is preliminary data that suggests that antihistaminic drugs may be beneficial (67). Milder anti-inflammatory agents, such as antioxidants and natural modulators of cellular and tissue stress, may be effective in treating Long COVID (70). Vitamin C as supplemental treatment has shown some positive effects on Long COVID patients. It may increase immune function and assist the body's own ability to return to homeostasis, it seemed to alleviate symptoms of fatigue and exhaustion and increase subjective life quality (52). Coenzyme Q10 and D-ribose have also shown some positive effects, but haven't been thoroughly studied (79).

Anticoagulation and antiplatelet therapy can be used for thrombotic issues during Long COVID. In one study, patients receiving triple anticoagulant medication reported complete symptom regression (79). Nattokinase is also somewhat popular and has shown an effect as biological antiplatelet drug derived from soy beans during the fermentation process (73). Statin therapy has also been discussed as optional treatment for endothelial dysfunction and endothelitis (95). Nevertheless, thromboembolic prophylactic therapy is not generally recommended (69).

Probiotics showed a positive effect on Long COVID symptoms like fatigue and memory loss as well as GI symptoms. SSRIs are being considered as a therapeutic option for individuals with GI and neurological symptoms, as they influence serotonin levels and the gut-brain axis (74). The effect of other serotonergic substances are currently under investigation (e.g. fluvoxamine) (73). Prebiotics can also be beneficial regarding GI manifestation and support rebuilding a healthy gut microbiome (76).
PICS of COVID-19 patients can be treated with a few well-established drugs, namely RAAS blockers, statins, glucagon-like peptide-1 receptor antagonists, dabigatran or ß-blockers – depending on individual symptoms (64). As there is evidence that the primary manifestation site of Long COVID patients with MCAS symptoms is in the intestines, a histamine-poor diet combined with the avoidance of known food allergens could be a therapeutic approach. In addition, histamine-receptor blockers could improve patient's clinical state (95).
Symptoms of dysautonomia and POTS can be treated relatively well using pharmacologic and non-pharmacologic methods. Increased salt intake and water consumption, compression stockings, ß-blockers, clonidine, ivabradine, verapamil, pyridostigmine, methyldopa or droxydopa and especially fludrocortisone seem to alleviate all dysautonomia symptoms, also those affecting the GI tract (57,64,73,74,91). Exacerbating factors like warm surrounding temperatures, prolonged standing and large meals should be avoided (57,65). To minimise the risk of orthostatic intolerance, regular aerobic exercise should be performed in non-upright positions, such as swimming or using a recumbent ergometer, as well as resistance training (65). Pyridostigmin should be used for patients suffering from dysautonomia and constipation, due to its peristaltic effect (74).

Currently, as with many other Long COVID symptoms, fatigue is recommended to treat symptomatically (86). Although there are some promising therapeutic approaches, there is

no universal strategy to treat Long COVID. Off-label medication to apply for fatigue symptoms may be naltrexone and nicotinamide adenine dinucleotide – or NAD. These two compounds have both shown positive effects on long-term fatigue (56). Naltrexone is a non-selective opioid-antagonist and acts as a glial cell modulator in the brain and has been widely used off-label to treat chronic inflammatory diseases like Mb. Crohn and others. In low doses it is used for the treatment of fibromyalgia, multiple sclerosis, CRPS and ME/CFS. This may be a meaningful pharmacological approach to treat neurological Long COVID, as it is said to improve a variety of symptoms associated with Long COVID (56,57,66). It is also broadly available and affordable and has few side effects (57). In addition to that, especially methods like cognitive behavioral therapy, graded-exercise therapy, acupuncture and abdominal tuina may help control ME/CFS symptoms, mostly in a rehabilitation setting. Pharmacologically, rintatolimod, enzyme Q10 and NADH, or the Staphypan Berna vaccine showed positive effects on ME/CFS symptomatology (64). Hyperbaric oxygen therapy improved fatigue and the neurocognitive function of patients (67). In case series, prednisolone also showed positive effects on neurological Long COVID symptoms (67). Melatonin may also be added as supplementary therapy, especially for patients suffering from sleeping disturbances, fatigue and brain fog (52). Different forms of neuromodulation have been investigated for treatment of acute and Long COVID. As brain areas involved in memory, fear and stress response appeared altered in Long COVID patients, Vagal Nerve Stimulation may be a promising therapeutic option for patients suffering from neurological manifestation (50). VNS has shown to positively affect these brain areas, as well as exerting an anti-inflammatory effect (50). In a pilot study, patients receiving VNS experienced reduction of nine Long COVID symptoms compared to patients receiving placebo stimulation (50). Stellate ganglion block can be helpful with a variety of Long COVID symptoms, like cardiopulmonary, dysautonomic and neuropsychiatric manifestation (57,79). It is currently used to treat anosmia, depression and anxiety in patients with PTSD and for neuralgic pain syndromes. As sympathetic overactivation is thought to play a role in long-term inflammation it could be a future treatment strategy of Long COVID. In one study, patients with smelling dysfunction reported the highest rate of symptom improvement after stellate ganglion block compared to other therapeutic options. In another small cohort study, Long COVID patients reported a reduction of at least one symptom in 86% of participants, and 61% even reported total symptom relief (57).

For cognitive impairment, strategies such as pacing, environmental modifications, the use of assistive devices, and restorative cognitive training may be employed to support functional improvement (65).
Persistent anosmia is currently managed by structured olfactory training (69). The use of corticosteroid sprays and vitamin A drops can be helpful (57). Intranasal insulin sprays have been proposed as alternative because of its capacity of olfactory mucosal regeneration (91).
For psychological and psychiatric disorders regarding Long COVID, patients should be offered pharmaceutical as well as psychological treatment. Mindfulness-based stress reduction may offer therapeutic benefits in alleviating overall stress, anxiety, depression, and sleep disturbances. Additionally, structured exercise training has been associated with reductions in psychological distress (65).
Schieffer and Schieffer suggested a multidimensional strategy, targeting primary communication pathways involved in Long COVID symptomatology – the RAAS-bradykinin pathway, cholesterol metabolism and the gut microbiome. AT1 receptor blockers help restore balance within the RAS–bradykinin axis, while statin therapy enhances endothelial function and produces a range of anti-inflammatory effects, collectively activating immunomodulatory pathways. In combination with a low-histamine and anti-allergen diet to restore a healthy microbiome and limit mast-cell degranulation, Long COVID could be treated from different angles at the same time, possibly enhance successful treatment (95).

The most universal recommendation is a combination of multidisciplinary rehabilitation, pacing and self-management for treatment of Long COVID patients (57). The therapeutic goal should be symptom relief and avoidance of chronification (69). Promotion of sleep, pain relief, circulatory support, measures to reduce stress and relaxation, strengthening of personal resources, support of adequate coping behaviour (e.g. neither excessive demands nor inadequate avoidance of activities) as well as support through suitable aids and socio-medical measures are the major goals of therapy (69). The CDC recommends a “personal medical management plan” individually designed for Long COVID patients by their treating doctors, that focuses on the improvement of symptoms and life quality (63). Generally, Long COVID patients should be treated in multidisciplinary teams. These could consist of cardiologists, gastroenterologists, pulmonologists, neurologists, psychiatrists and almost any specialist department, depending on the individual clinical presentation. They

should also include physicians, dieticians, psychologists and social workers as well as physiotherapists and speech and language therapists (65). Patients should be introduced to multidisciplinary teams at an early stage of disease, to assess the need for rehabilitation, planning of further interventions and constantly reevaluating therapeutical possibilities (65). In summary, treatment options mainly focus on symptomatic therapies, patient-centered management and rehabilitation (57).

3.6 Disease progression, prognosis and rehabilitation

Most patients suffering from Long COVID are substantially limited in living their daily life (51). The health-related life quality of Long COVID patients can be compared to chronic post-surgical pain following spinal procedures (72). The UK Office for National Statistics published findings in 2023, showing that approximately 1,5 million UK citizens have been adversely restricted in their day-to-day lives due to post-COVID-19 condition (59). Chronic abdominal symptoms are reported to limit life quality to a great extent in Long COVID patients (76). Individuals with musculoskeletal pain were the group most restricted in their daily work routine (72). Long COVID patients generally experience more economic hardship and existentially threatening problems following their disease (56).

Individuals with long COVID in low- and middle-income countries often receive restricted or no care, primarily due to limited health care systems, poorly developed primary care infrastructure, and competing healthcare demands posed by the high prevalence of other diseases. Even in high economically developed countries, the most socioeconomically disadvantaged populations—characterised by more comorbidities, limited access to healthcare, and challenges in resuming full-time employment—are disproportionately affected most severely by Long COVID (88). The fact that low-income countries are more likely to have a lack in social protection measures only aggravates this gap in receiving adequate care (88). Additionally, vaccination rates in low-income and middle-income countries are much lower than in the western world, which causes higher susceptibility to infection and Long COVID. Future and current therapies for Long COVID are rarely available, and if they are, it may not be affordable for the affected population (88).

In multimorbid, elderly patients in long-term-care facilities, Long COVID is associated with higher risk of falling, increased frailty and pain, reduced life-quality and higher rates of exacerbation of preexisting illnesses (89). Still, patients hospitalised for COVID-19

exhibit one- to two-year outcomes comparable to those of individuals hospitalised for sepsis, influenza, or diagnosed with post–intensive care unit syndrome, suggesting that some post-COVID condition manifestations may be attributable to the severity of the underlying infectious illness requiring hospitalisation (68).

One study shows, that 85% of Long COVID patients with persistent symptoms two months after initial infection still present as symptomatic one year after – recovery is a weary and long-lasting process (79). About 7.8% to 17% still report symptoms after 12 weeks, other sources report 24% of Long COVID patients still showing signs of clinical disease two years later (81). The vast amount of patients make a full recovery eventually. About 65% of all Long COVID patients show a good recovery within seven months of follow-up period (50). Post-Omicron Long COVID tends to resolve faster than other strains of initial SARS-CoV-2 infection (81). Guidelines recommend physical, mental and psychological rehabilitation in addition to nutritional and pharmacological interventions – except for patients with irreversible lung damage. For POTS and ME/CFS, physical exercise rehabilitation should be adapted to the individual's capabilities and needs (56,57).

Many Long COVID symptoms limiting life quality can successfully be handled via rehabilitation, including neurological, pulmonological, cardiovascular and GI limitations (52). Rehabilitation can be pursued provided that acute symptoms caused by COVID-19 should have subsided for at least two days before transfer. The respiratory and circulatory situation should be stable enough that transfers back to the acute care unit are not to be expected (69). The most common symptoms requiring rehabilitation in Long COVID patients are neurocognitive symptoms, dyspnea and exercise intolerance, autonomous dysregulation and psychiatric disorders like anxiety and depression (65). Rehabilitation is one of the major components of a successful treatment and improvement of functional outcome in Long COVID patients (65). This is especially true for pulmonary rehab, which has proven to significantly improve persistent pulmonary symptoms post-COVID (52). Pulmonary rehabilitation has shown to improve respiratory function, exercise capacity, balance and anxiety or depression in Long COVID patients compared to usual hospital care (57,90). Respiratory physiotherapy (e.g. specific inspiration training) and sports/movement therapy are the core components or pulmunologic rehab (69). Cognitive motor training and exercises appear to enhance cognitive performance. Fatigue and physical post-exertional malaise can be effectively improved by training and physical

activity, though patients should not exceed their personal limits (90). Too harsh training can trigger massive worsening of symptoms, which is why individual training plans according to patients' clinical presentation must be worked out. "Pacing" is a type of training, where patients do not go beyond their individual threshold, and slowly try to increase their performance (52). It is a form of well-dosed, supervised physical activity and individually appropriate energy management. It can be applied for physical and cognitive impairment. Pacing is designed to manage fluctuating and diminished energy levels by modifying or regulating the intensity and duration of activities to align with the individual's current capacity. This may involve using energy conservation techniques such as prioritising tasks, delegating responsibilities, using assistive devices and alternating periods of activity with rest in order to manage daily demands. Activity pacing strategies may also be employed, emphasising the setting of activity goals and the gradual increase in activity levels over time (57). Implementation of a pacing protocol led to significant reductions in the average number of post-exertional malaise episodes, along with improvements in life quality and physical activity tolerance (91). Keeping this in mind, post-exertional malaise should be ruled out before starting conventional physical rehabilitation exercises (65).

Exercise-based rehabilitation is a core component of long-term recovery from Long COVID. It is recommended for treating fatigue, exercise intolerance, breathlessness, musculoskeletal pain, sleep disturbances and mental health challenges in affected individuals. It should include aerobic and resistance training and/or respiratory muscle training. Although there is limited data from RCTs, it has been shown to enhance respiratory function, reduce fatigue, increase functional capacity and muscular strength, and promote overall quality of life and psychological well-being (65). Psychological support also plays a very important role in the recovery process (52). Self-activities including muscle relaxation exercises and mental training had an impact on anxiety in rehabilitation programs (90). The use of neurorehabilitation proves to be effective for treating neurocognitive and psychological impairments (91). This should only be conducted by skilled neuropsychologists (69).

Telerehabilitation and educational intervention has also proven helpful for post-COVID-19 condition patients, as some cannot attend rehab outside of their homes or are not able to perform tasks sufficiently (65). This way affected individuals can still participate in rehabilitation programs without having to leave their homes, and can organise their time

and energy as individually possible. It has been shown to be helpful for dyspnea, functionality overall stress and life quality (57,65).
Rehabilitation should be scheduled for a minimum of three weeks' time to achieve sustainable progress (40).

Long COVID can have very serious economic impacts as well, as it hinders affected individuals from working for a prolonged period of time. Long-term effects of the virus impose substantial burdens on healthcare utilisation, workforce participation and employment (57). A US analysis showed that about 25% of Long COVID patients in 2021 reported that their condition negatively impacted their working hour load or their employment status. On average, Long COVID patients worked 50% less than healthy individuals with no history of COVID-19 (53). In an earlier source from 2020, 45,2% of Long COVID patients had reduced work hours because of their illness, and 22,3% were not working at all due to Long COVID (52,53). In a cross-sectional study from Klein et al, 50% of all participants suffering from post-COVID condition reported negative impact on their current employment situation (83). By 2022, it has caused around 3,5 million people to quit their jobs (53). The Economist Impact published a report in April 2024, stating that Long COVID has caused a loss of 1,5 billion work hours in total, resulting in costs above 152 billion US dollars (53). In the United States, for example, the annual economic impact is estimated to be as high as $2.6 trillion dollars (57). Because of its long duration and no causal therapeutic options, the estimated cost of this disease will mount to over $3 trillion US dollars (53,85). Fatigue emerged as the primary symptom associated with long-term functional decline and reduced work capacity, followed by depressive symptoms and cognitive impairment (68).
Evidence from research indicates that social factors have influenced both how widely vaccines were administered and how infection rates varied throughout different stages of the pandemic. Protective factors and risk factors therefore may not have been evenly distributed among the population, causing varying courses and durations of disease (97). Research from the UK has shown that people inhabiting more deprived areas are at higher risk of developing Long COVID. Asian individuals living in the UK had lower chances of post-COVID condition after infection (97).
Long COVID is a serious public health concern, as disease duration is variable, no causal therapy is available, and patients are likely to occupy health care institutions for many months in different sectors (e.g. hospitalisation, specialised medical services,

rehabilitation, psychological help etc.) (52). The multidisciplinary dimensions of Long COVID treatment cause high input of resources and work for minimally satisfying results in patient outcome (52). Public health efforts that are specially designed - such as customised health information and vaccination initiatives developed in collaboration with local communities - may contribute to reducing health disparities. In parallel, introducing specialised healthcare services could be especially beneficial in the regions most severely affected (97).

4 Discussion

The growing recognition of Long COVID as a post-infectious, multisystem condition has highlighted the urgent need for a standardised clinical definition. The abundance of different definitions and diagnostic criteria makes it very hard for clinicians and medical staff to correctly identify and categorise Long COVID patients. A universal framework is critical to distinguish Long COVID from prolonged recovery, unrelated newly occurred diseases or complications of pre-existing comorbidities. In clinical practice, the absence of objective diagnostic tests forces healthcare providers to rely heavily on exclusion diagnostics, increasing the burden on both patients and physicians.

According to the WHO, Long COVID - termed post-COVID-19 condition - should be diagnosed if symptoms persist or recur three months after an initial SARS-CoV-2 infection, last for at least two months, and cannot be explained by an alternative diagnosis. The NASEM definition tried to fill in a few lacking patient-related factors and information to the WHO definition, which makes it very broadly defined. This could again lead to difficulties in health care, as too many patients may be diagnosed with Long COVID.

As described above, Goldenberg came up with an augmented definition, excluding post-COVID-19 organ diseases and morphologic pathologies from the Long COVID definition. Undoubtedly, patients may suffer from prolonged symptoms due to direct or indirect organ damage because of acute COVID-19. These medical implications shouldn't be ignored – but they should not be included in the definition of Long COVID in the strictest sense. Pathophysiology of these two types of medical sequelae are very different, and throwing them into one big pot may be hindering future research in the field to come up with concrete utilizable clinical data. In the course of this diploma thesis, I conclude that the term "Long COVID" (per definitionem), should be used only for clinical manifestations and symptoms that cannot be explained by other pathologies. Post-COVID organ damage

like lung fibrosis or myocarditis causing prolonged symptoms and delayed recovery should be labelled otherwise, and coming up with a new term and definition is necessary. As Goldenberg quotes: “Long COVID is not blood clots, myocarditis, multisystem inflammatory disease, pneumonia, or any number of well characterised conditions caused by COVID-19” (68). It is a separate, newly discovered and poorly understood disease entity, which needs further investigation and research to be properly comprehended. Goldenberg also states, that the diagnosis of Long COVID should rather focus on clinical criteria like duration and symptomatic spectrum (like already in practice for other disorders, e.g. ME/CFS, fibromyalgia and IBS), than on specific pathological findings (68). Naturally, simultaneously occurring disease entities like ME/CFS or POTS should be diagnosed and treated – but independently form Long COVID diagnosis. If a patient fulfils disease criteria for an already existing illness, diagnosis and treatment should be tailored accordingly.
Many other definitions include this requirement as well. Like this, doctors as well as patients can receive an adequate treatment – for either one or the other of the two conditions.

Biochemically, chronic immune activation appears central to Long COVID pathogenesis. No clinically significant biomarker has been identified throughout research, but this could be due to vague inclusion criteria of patients in studies and other restrictions regarding currently available research data. Persistent elevation of cytokines has been repeatedly linked to hallmark symptoms such as fatigue, cognitive dysfunction, and respiratory complaints. TNF-alpha, for example, shows a strong association with post-infectious fatigue and chronic cough, while elevated CRP correlates with multisystem involvement, including pulmonary and neurological manifestations. Notably, La/SS-B autoantibodies have been identified in cases with GI symptoms, suggesting potential autoimmune components in symptom development.
Long COVID - particularly when manifesting neurologically - may present with delayed onset, lingering symptoms for over two years, and unknown long-term consequences. Recent findings suggest elevated NFL and glial fibrillary acidic protein as biomarkers for neurocognitive Long COVID in affected individuals, indicating actual neuronal damage and astrocyte dysfunction. Additionally, lowered cortisol in patient serum was also identified in neurologic Long COVID patients. These biological signatures underscore a

potential risk for neurodegenerative disorders in the future and highlight the urgent need for validated biomarkers to support early detection and intervention.
The biomarkers most frequently elevated in Long COVID patients included CRP, IL-2, IL-4, IL-6, IL-10, IL-17,TNF-α, IFN-γ, CCL-2, D-dimer, LDH, leukocytes and ferritin.
As a result - for definitive diagnosis no one single biomarker is available. Nevertheless, clinicians have some resources to reinforce their suspected diagnosis, if they surmise Long COVID syndrome in a patient. Besides biomarkers available, other tools and scores are available for a further categorisation of patients.

Despite these advances, the diagnostic ambiguity surrounding Long COVID poses significant clinical and social challenges. One of the major clinical hurdles remains the absence of objective diagnostic tools - practitioners are left with subjective questionnaires etc. to work with, and must systematically eliminate other well-defined conditions such as myocarditis, thromboembolism, or pulmonary fibrosis before suspecting Long COVID. The process of diagnosis by exclusion goes hand-in-hand with a significantly increased workload for doctors and makes treatment of these patients a weary and ambiguous process. This once more reinforces the argument made by Goldenberg and others who propose that diagnostic criteria for Long COVID should resemble those used in syndromes like ME/CFS, fibromyalgia, or IBS - focusing on the persistence of systemic symptoms (fatigue, post-exertional malaise, cognitive and sleep disturbances) and excluding organ-specific pathology.

Currently, there are no universally accepted curative treatments for Long COVID, but several therapeutic approaches have shown promise. Given the heterogeneous nature of the syndrome, treatment is largely symptom-based and multidisciplinary. But as accuracy in diagnosis increases and different subtypes of Long COVID can be identified, therapeutical options can be tailored as good as possible to each individual patient and his or her needs. Rehabilitation is central to managing physical fatigue, pulmonary symptoms and exercise intolerance. Graded exercise therapy and pacing strategies may help patients with fatigue and even post-exertional malaise when closely monitored. To prevent symptom exacerbation, each patient should be reevaluated regularly and physical rehabilitation should be considered only if post-exertional malaise can be ruled out before starting therapy.

Neurocognitive symptoms such as brain fog and memory impairment are being addressed through CBT, occupational therapy and cognitive rehabilitation programs. In some cases, medication, though robust data on efficacy are still emerging, can be administered as off-label therapy. Pharmacologic interventions target underlying pathophysiological processes and should be administered according to symptom presentation. Low-dose corticosteroids, antihistamines, or SSRIs have been trialed to modulate persistent inflammation, autonomic dysfunction, or mast cell activation, with varying success. Low-dose naltrexone has shown promising results for patients with fatigue during Long COVID and can additionally be used for patients simultaneously suffering from ME/CFS.
For patients with autonomic symptoms or POTS, treatment with beta-blockers, clonidine, fludrocortisone, or midodrine may offer symptom relief.
Mental health support is critical, as many patients experience anxiety, depression, or PTSD following the acute illness and during the protracted course of recovery.
Immunomodulatory treatments are under active investigation. Given the consistent elevation of cytokines like IL-6 and TNF-α in affected individuals, therapies targeting these pathways - such as IL-6 inhibitors or TNF blockers - may offer future therapeutic benefit. However, further clinical trials are required before widespread adoption.
Ultimately, effective management of Long COVID requires personalised care based on the patient's symptom profile, comorbidities, and functional status. Ongoing research into biomarker-driven subtyping may enable more targeted therapies in the near future.
Currently, rehabilitation has the greatest significance in the treatment of Long COVID patients – medication can only be used as amplifying “try-out” therapies, to assist recovery.

From a socio-economic perspective, the implications are profound. Many Long COVID patients suffer long-term physical or cognitive impairment, making it difficult to return to previous employment. Prolonged duration of the disease leading to extended sick leaves, repeated medical consultations, and lack of rehabilitative infrastructure contribute to financial strain, potential job loss, and increased healthcare costs. Many patients cannot return to their previous occupation to full extent. This situation is especially precarious for individuals with limited access to social support systems.
On a global scale, these challenges are even more severe in low- and middle-income countries. As already shown by other scientific works, there is an urgent need to expand Long COVID research to these settings to ensure that case definitions, treatment

guidelines, and future therapeutics are applicable and accessible across diverse populations. Including low-income populations in clinical trials and ensuring equitable distribution of emerging treatments must be prioritised to avoid repeating patterns of marginalisation witnessed during the acute phases of the pandemic.

At a broader level, it is important to consider Long COVID within the context of global health preparedness. The increasing frequency of zoonotic spillovers, driven by environmental changes such as deforestation, climate change, urbanisation, and intensified global mobility, strongly suggests that pandemics of similar or greater scale may recur in the coming decades. Understanding post-viral sequelae like Long COVID today not only enhances individual patient care but also prepares healthcare systems for future outbreaks of emerging respiratory viruses.

In conclusion, Long COVID represents a complex interplay of infectious, immunological, neurological, and psychosocial factors that challenge traditional diagnostic frameworks. The need for interdisciplinary research, internationally harmonised definitions, biomarker discovery, and equitable treatment access - especially in economically less developed countries - is urgent. Especially neurocognitive manifestations of Long COVID are affecting societies around the world, as it is mostly characterised by a delayed onset, a long illness duration and an unknown prognosis for the future. Research is urgently necessary on this particular field, as there may be an increased long-term risk for neurodegenerative diseases in former Long COVID patients due to similar neuropathology discovered. Addressing these gaps will be crucial in developing targeted interventions and minimizing the long-term global burden of this post-pandemic syndrome.

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Appendix

4.1 Unite to Fight 2024 – Transcript

Prof. Daniel Altmann (Imperial College London) – Immunology of Long Covid

- ➔ "Decoding the unknowns in long covid" – Altmann, Boyton
- ➔ "Long COVID in low-income and middle-income countries: the hidden public health crisis"

Long Covid symptoms: fatigue, postexertional malaise, headache, brainfog, sleep disorders, hairloss, anxiety, depression, concentration difficulties, cough, exanthema, dyspnea, vertigo, chest tightness.
Possible mechanisms: organ damage in target issue, persistent virus or antigen reservoirs (driving T-cell exhaustion?), reactivation of EBV, changes in inflammatory activation, systemic immunity, vascular endothelium dysfunction, mast cell activation,…
Gold standard for detection of virus persistence: antigen diagnostics in gut biopsies

Can you get vaccinated (covid and others) while you are recovering from LC, or could this backfire and increase or trigger new symptoms?

- Keep up vaccinations, because alternative infections are much worse!

Dr. Johan van Weyenberg (Rega Institute for Medical Research, BE)

- ➔ Menezes et al (Lancet Microbe 2024) – welche Biomarker erhöht in Long Covid? (antisense-RNA!!)

Diagnostic biomarkers

- ➔ Viral persistence? Biopsy of CSF/respiratory/intestinal/blood
- ➔ Biomarkers for treatment effectivity
- ⇨ Transcriptome!! (mRNA which is transcribed during COVID-infection)

Therapeutic option: *Paxlovid* off-label study? Average 32% drop in total symptoms (unpublished, grass root study)

Prof. Carmen Scheibenbogen (Charité Berlin) Head of Immunodeficiency – ME/CFS as part of the post-COVID spectrum

- ➔ "A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity"
- ➔ "Fighting Post-COVID and ME/CFS-development of curative therapies" – Scheibenbogen C. et al

Reasons for ME/CFS: hypoperfusion through diverse causes, e.g. autoantibodies to GPCR, RDS, inflammation, autonomic dysfunction, endothelial dysfunction, impaired RBC deformability, low preload.. => causes muscle pain weakness + brain fog through mitochondrial dysfunction (because mitochondria are not sufficiently provided with energy; toxicity to mitochondria is the effect)

Dr. Rob Wüst (Vrje University Amsterdam) – skeletal muscle function & post-exertional malaise in patients with Long-COVID

- ➔ Appelmann et al 2024 (Nature Comm)

Post exertional malaise (=PEM): within 48h, worsening of general symptoms or development of new symptoms = physical/cognitive/mental exertion; can last for days-months! => exercise is NOT recommended for post-COVID patients!! Individual thresholds of exercise levels in patients

- Diagnosis of post-exertional malaise with DSQ-PEM questionnaire (no blood or imaging biomedical markers available)
- Metabolic and mitochondrial dysfunction in Long COVID worsen after induction of post-exertional malaise

Microclot theory in long COVID (as explanation for PEM): amyloid-containing deposits in muscle fibers, increasing after induction of PEM

What can we do to maintain muscle function with long covid?

- Physiotherapy & ergotherapy can help with recovery without reaching the personal PEM level

Prof. Dr. Bernhard Schieffer (Medicine University Marburg) – Targeting the HDL Proteome for the Treatment of Post-COVID Syndrome

- ➔ "Long COVID: mechanisms, findings, … (?)"
- ➔ "The race for ACE: targeting ACE… (?)"
- ➔ "The rationale for the treatment of long-COVID symptoms – a cardiologist's view" – Elisabeth Schieffer, Bernhard Schieffer
- ➔ "Statin use is associated with lower disease severity in COVID-19" – Brand et al

Treatment of Long COVID: (from cardiologist's point of view) pretreatment with statins enhances prognosis! (lower risk of severe COVID-19 infection)
HDL as anti-inflammatory actor!!! (modulates immune system and reaction)

CBT/GET paradigm? (-> recherchieren!)

Prof. Wesley Ely (Vanderbuilt Medical Center, Nashville) – Immunomodulation in Long Covid

- ➔ REVERSE-LC study?

Prof. Akiko Iwasaki (Yale University) – Immunology of post-acute infection syndromes

- ➔ Iwasaki & Putrino (The Lancet Infectious Diseases, 14.02.2023)
- ➔ MY-Long COVID Study - <Klein et al (2023 Nature)
- ➔ "Sex differences in symptomology of Long Covid"

Other viruses causing acute infection syndromes: Dengue, Polio, SARS, Chikungunya, EBV, Coxsackie B, VZV, Influenza,…

Core symptoms: severe fatigue, exertion intolerance, neurocognitive impairment, sensory impairment, flu-like symptoms, unrefreshing sleep…
4 possible root causes:

- Viral reservoir
- Autoimmunity
- Tissue damage and dysfunctions
- Latent virus reactivation

+ lowered cortisol levels in Long Covid patients!

Female predominant symptoms: dizziness, body temperature, sexual dysfunction (males), hair loss (females) => sex differences!

Reactivation of EBV in Long Covid patients!

Hormonal dysregulation in Long Covid patients! (low testosterone in female patients as predictive marker?)

Dr. Michael Kacik (Münster) – Vascular regulation mechanisms in post COVID disease and ME/CFS

- Endothelial dysfunction and microcirculatory disorders in long COVID e.g. capillaries
- Venous vascular dysfunction in lower extremities and the trunk (venous system strongly regulated by sympathetic nervous system and stimulated by gravity => orthostatic intolerance!)

⇨ Therapy of vascular dysregulation improves various symptoms significantly