VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final Thesis

Difficult Cases of COVID Infection: Case Presentations and Literature Review

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Content

1. KEYWORDS & ABBREVIATIONS

Keywords: COVID-19, pandemic, pneumonia, respiratory failure, mutation, therapeutic management and prevention, vulnerable groups

Abbreviations	**Meaning**
COVID-19	Coronavirus disease 2019
ECMO	Extra corporal membrane oxygenation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organisation
RNA	Ribonucleic Acid
ACE2	Angiotensin converting enzyme
VOC	Variant of concern
VOI	Variant of interest
TMPRSS2	Transmembrane protease serine 2
NAAT	Nucleic acid amplification test
PCR	Polymerase chain reaction
ARDS	Acute respiratory distress syndrome
SIRS	Systemic inflammatory response syndrome
ICU	Intensive care unit
MPRO	Main protease
VUH	Vilnius University Hospital
PLT	Platelets
MCV	Mean corpuscular volume
HB	Haemoglobin
AST	Aspartate transaminase
ALT	Alkaline phosphatase
WBC	White blood cells
CRP	C-reactive protein
NT-pro BNP	N-terminal pro b-type natriuretic peptide
ECG	Electrocardiogram
SpO2	Oxygen saturation
NIH	National institute of health
BP	Blood pressure
IgM	Immunoglobulin M
IgG	Immunoglobulin G
QD	Once a day
BID	Twice a day
TID	Three times a day
QID	Four times a day

2. SUMMARY

The COVID-19 disease presents with a wide range of clinical symptoms, from asymptomatic or mild disease to severe illness with respiratory failure and multiple organ dysfunction. The pathophysiology of COVID-19 involves a complex interaction between viral factors and the host immune response, which can lead to systemic inflammation and damage to multiple organ damage.

Several risk factors for severe disease have been identified, including advanced age, cardiovascular disease, obesity, diabetes and pregnancy. In addition, some population groups, such as ethnic minorities and those of lower socio-economic status, may be disproportionately affected. In severe cases of COVID-19, respiratory failure is a common complication and might require mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Other complications can affect almost all systems of the human body and lead to multiple organ failure.

Treatment options for COVID-19 have evolved during the pandemic. At the beginning of the pandemic, supportive care was the main treatment option. However, several antiviral and immunomodulatory therapies have been developed and used in clinical practice.

Two clinical cases of patients with COVID-19 will be used to illustrate the topic, focusing on the course of the disease and the treatment of symptoms. These cases can be considered as classic examples of what a SARS-CoV-2 infection looks like in the Omicron era of COVID-19.

3. INTRODUCTION

In recent years the COVID-19 pandemic has had a profound impact on societies around the world. And while it is now under better control, the virus had not disappeared, and people are still suffering severely. The pandemic was a big challenge for every individual, with deep social cuts in our daily life's but it was an even greater challenge for the whole healthcare system. Doctors and nurses were working beyond their limits to treat the patients and it was realized soon that a COVID-19 infection was much more than just a respiratory infection. And the challenges have evolved with the new mutations.

For this reason, it is important to provide a general understanding of how the different SARS-CoV-2 mutations have evolved over the years and how they have affected the course of the pandemic and the impact on our society. We will therefore also focus on treatment outcomes and vulnerable groups. Some other questions need to be answered as well. Where and how

could the virus develop from? How does it enter our body and how does it affect it? How to diagnose the disease correctly and what impact does the virus have on the course of the pandemic?

Despite advances in treatment, difficult cases of COVID-19 continue to challenge healthcare providers. In some cases, treatment options may be limited by factors such as drug availability, drug-drug interactions or contraindications. In addition, the long-term effects of COVID-19 on survivors are still not well understood, and ongoing monitoring and care will be necessary for these patients.

4. ORIGIN AND DEVELOPMENT

COVID-19 is an acute infectious respiratory disease caused by SARS-CoV-2. Initially, there were various theories about the origin of the SARS-CoV-2. Much unconfirmed information and rumours were circulated. In July 2022, the Magazin "Science"[1] published a scientific article which confirmed that the Huanan seafood wholesale market in Wuhan was the early epicentre of the COVID-19 pandemic. The virus was transmitted over from wild animals which were sold on the market into people. The study showed that the first cases of the COVID-19 infections where all centred in this market. As shown on the diagram, the cases were divided into two groups. People who had direct contact with the market and those who had no direct contact with the market. The results showed that in the group of people who had no direct contact with the market but were diagnosed with the virus, all had a geographic center close to the market. With this information and the results of the study, the origin and evolution of the virus could be confirmed.

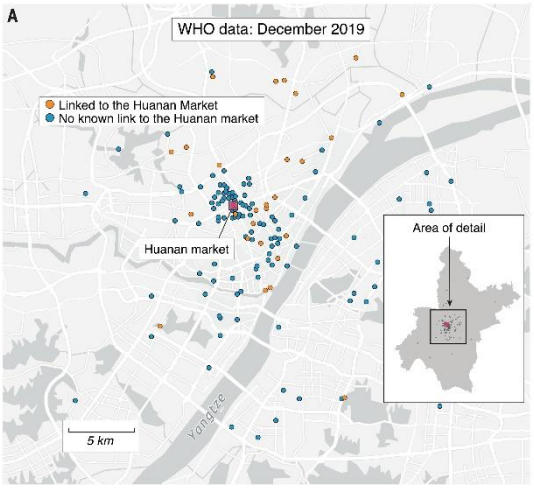


Figure 1: Origin of the SARS-CoV

The virus has subsequently spread rapidly around the world and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. On that day more than 118,000 cases were reported in 114 countries and 4,291 people died.[2]

[1] (Michael Worobey, 2022)
[2] (Ghebreyesus, 2020)

5. ETIOLOGY

The structure of the SARS-CoV-2 is built up with an enveloped and single stranded ribonucleic acid. It is non-segmented and has a positive-sense RNA. The viral genome encodes four structural proteins including spike proteins which facilitate the entry of the virus by attaching to the ACE2 receptor on the surface of the host cell. Additionally, the envelope protein, which is needed to hold the viral particles together, a matrix protein which gives the virus its structure and the nucleocapsid which packages the viral genome into a helical ribonucleocapsid. [3]

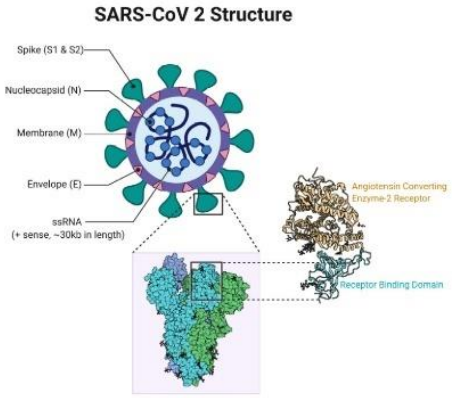


Figure 2: SARS-CoV-2 Structure

Figure 3: SARS-CoV-2-Variants

With time mutations can occur in the genome of the virus which cause new variants and they can show new characteristics. That causes the virus to spread faster, cause more severe diseases and to make it tolerant to drugs or vaccines. Since the beginning of the pandemic, several different mutations developed. Mutations can be categorized in variants of concern (VOC) and variants of interest (VOI).[4] Variants of concern have clear evidence for significant mutations in the spike proteins which cause an increase binding affinity and at the same time they can be linked to a rapid spread in human populations. These are the ones which were dominant in the last years, and which can be seen on the table. Variants of interest could have the same impact as VOCs, but the evidence is associated with uncertainty. These mutations are for example Lambda or Mu.

Since the two following cases are based on the SARS-CoV-2 Omicron variant, the thesis was focused on the VOC - Omicron variant. Further information about the other mutations will follow later. Omicron was first reported in 2021 and more than 30 mutations in the S protein were detected. With Omicron the number of cases increased a lot while the death rate remained

[3] (Hasoksuz, 2023)
[4] (Freund, 2021)

similar. The treatment guidelines remained the same. Due to the rapid spread of the virus, an immunity to this strain was a positive consequence. [5]

6. PATHOPHYSIOLOGY

But how does the virus enter the body and cause these symptoms? The pathogens are transmitted via aerosols and enter the respiratory tract while we breathe them in. The incubation time can vary between few days and two weeks.

The graph shows the pathogenetic process of SARS-CoV.[6] During the invasion of the virus the spike protein on the surface of the virus binds to the membrane protein angiotensin-converting enzyme 2 (ACE2). These are expressed on the surface epithelium of the lungs, heart and other organisms. Transmembrane protease serine 2 (TMPRSS2), found in respiratory epithelium than activates the spike protein. The movement of the virus into the cells of the host organism takes place through direct membrane fusion between SARS-CoV-2 and the host cell plasma membrane. After Endocytosis uncoating of the viral RNA occurs and is released in the cytosol of the host cell. Glycoprotein cleavage allows fusion of viral membranes with endosomal membranes and the release of viral RNA into the cytoplasm. Then the replication cycle starts. Enzymes like RNA polymerase or proteases, are virally induced by endosomal viral RNA. Later they release and replicate viral components. In the end endosomes with newly formed viruses are released via exocytosis.[7]

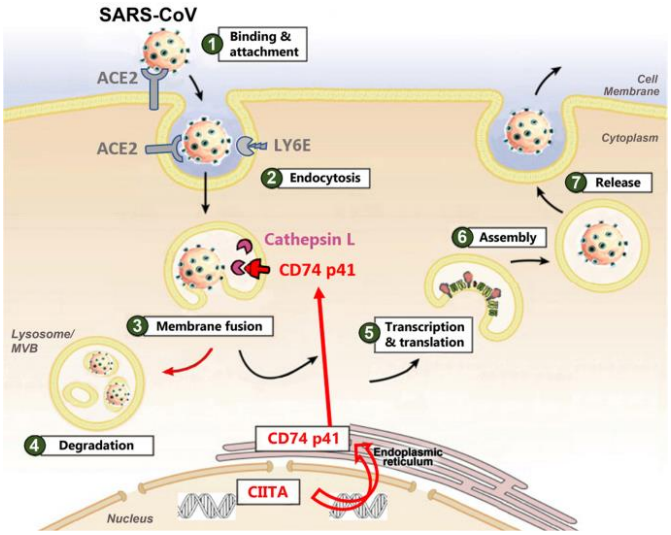


Figure 4: Pathogenesis of the SARS-CoV-2

7. DIAGNOSTICS

There are different ways how to detect SARS-CoV-2. The gold standard for detecting the virus is the nucleoic acid amplification test (NAAT) also known as PCR-Test. It has a very high sensitivity and specificity if it needs to detect the viral DNA. The viral RNA is transcribed into complementary DNA and then amplified to detect any SARS-CoV-2 genetic material. The graph below shows the ability to detect SARS-CoV-2 with diagnostic tests from exposure to

[5] (European Centre for Disease Prevention and Control , 2023)
[6] (Rafal Butowt, 2020)
[7] (Abdur Rauf, 2020)

recovery. On the vertical axis we can see the probability of detection while the horizontal axis shows time before and after the onset of symptoms. Depending on how long the time between infection and first symptoms is, the detection before the onset is quite unlikely. We can see that the highest probability to receive a positive PCR test is in week 1 to 3 after onset of symptoms. In that time, we have a high viral isolation in the respiratory tract. After week one IgG and IgM antibodies increase what makes it a very sensitive serological marker. After week 2 the PCR swab in the nasopharynx decreases and after approximately three weeks the PCR test appears mostly negative.

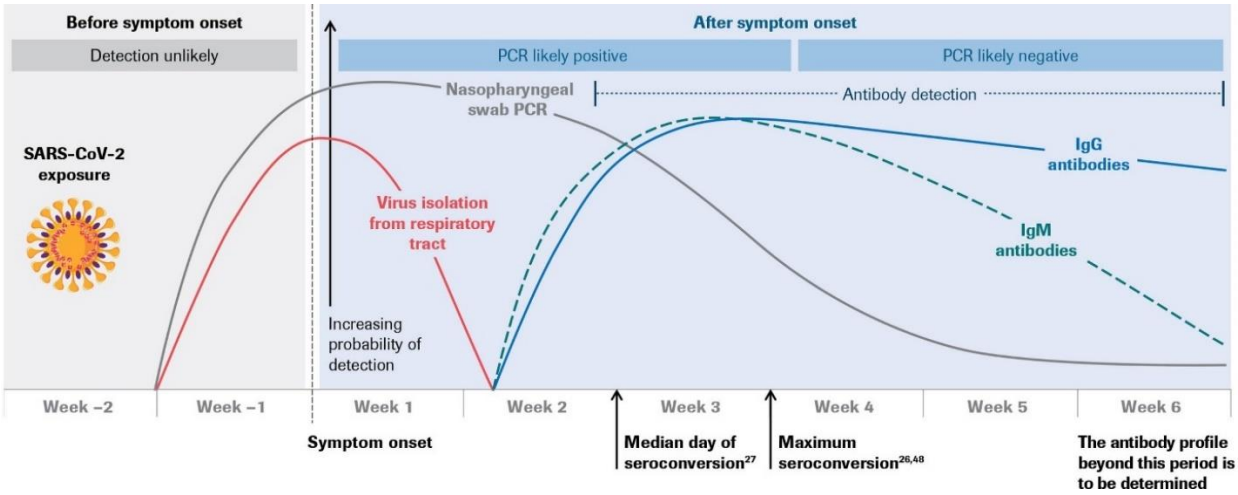


Figure 5: Ability to detect SARS-CoV-2 through diagnostic tests from exposure to recovery [8]

Another option is the antigen rapid detection test which directly detects SARS-CoV-2 antigens. It is less sensitive but much easier and cheaper to perform. Also, the results are available much faster. Therefore, it can be used as a public health tool for screening of vulnerable individuals, ensure social events or enabling economic recovery.[9]

[8] (Roche, 2023)
[9] (Amboss, 2023)

8. CLINICAL FEATURES, RISK FACTORS & COMPLICATIONS

The prevalence of COVID-19 infections between men and women is the same and the symptoms are mostly mild. Most of the time people present with symptoms like fever cough, shortness of breath, fatigue, shortness of breath, sore throat, rhinitis or loss of smell and taste. COVID-19 is caused by the SARS-CoV-2 and can cause a range of symptoms from mild to severe and it also differs depending on the mutation. It can even be asymptomatic.[10]

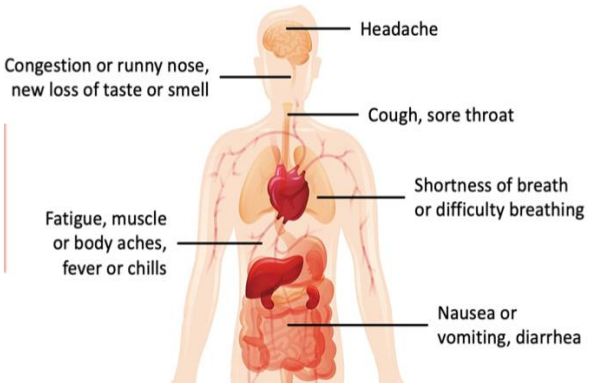


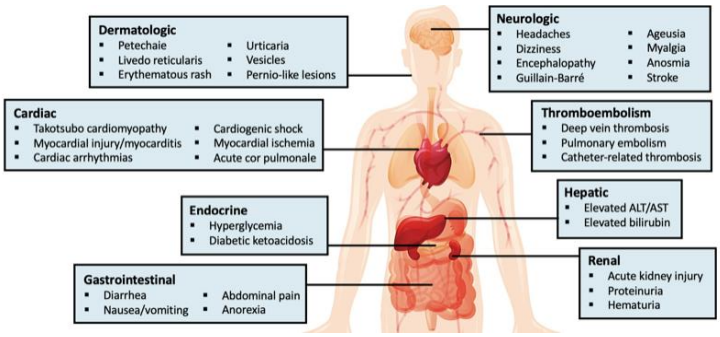
Figure 6: General symptoms

Some people with COVID-19 infection may develop severe illness that can lead to hospitalisation, intensive care unit admission and even death. Severe disease can be characterised by respiratory failure, sepsis and acute respiratory distress syndrome (ARDS).

Risk factors for severe disease include age, underlying diseases and certain demographic factors. Older adults are at higher risk of severe disease, as are people with underlying conditions such as heart disease, diabetes and lung disease. Further risk factors include obesity, pregnancy and immunosuppression.

Even though COVID-19 is well-known for substantial respiratory pathology, it was shown that it also results in several extrapulmonary manifestations. These conditions can be thrombotic complications, acute kidney injury, myocardial dysfunction and arrhythmia, hyperglycaemia and ketosis, acute coronary syndromes, gastrointestinal symptoms, hepatocellular injury, neurologic illnesses, ocular symptoms, and dermatologic complications. As we know ACE2, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in multiple extrapulmonary tissues. Consequently, direct viral tissue damage is a plausible mechanism of injury. Endothelial damage and thromboinflammation leads to dysregulation of immune responses, and maladaptation of ACE2-related pathways. This might all contribute to the extrapulmonary manifestations. [11]

[10] (Li L-Q, 2023)
[11] (Aakriti Gupta, 2020)



This figure shows the manifestations which can occur, and which systems are involved. As we can see it can affect almost all systems of our body.[12]

Figure 7: Clinical Manifestations

COVID-19 disease is divided in three phases. These are based on the progression of symptoms and the disease severity:

- Mild illness: This phase approximately lasts for up to 7 days after symptom onset. Symptoms during this phase can include fever, cough, sore throat, fatigue, body aches, and loss of taste or smell. In mild illness people do not have shortness of breath. They mostly recover at home with supportive care, such as rest, hydration, and over-the-counter medications to manage fever and pain. There is no imaging or lab test indication.
- Moderate illness: If symptoms worsen or persist beyond the first week, the disease may progress to the moderate phase. This phase can include shortness of breath, persistent chest pain or pressure, confusion or altered mental status, and low oxygen saturation. People may require hospitalization for supplemental oxygen and other supportive measures.
- Severe illness: Sometimes the disease can lead to the severe phase. It can be characterized by respiratory failure, sepsis, and multiorgan dysfunction. People in this phase may require intensive care unit admission or mechanical ventilation to support their breathing. Since other organs can also be affected, treatment may also include supportive measures for example for the kidney or liver.

It's important to note that not all people with COVID-19 will progress through all three phases, and some people may skip the mild or moderate phase and present with severe disease.[13]

[12] (Gupta. Nat Med. 2020;26:1017., 2020)
[13] (Health, Clinical Spectrum of SARS-CoV-2 Infection, 2023)

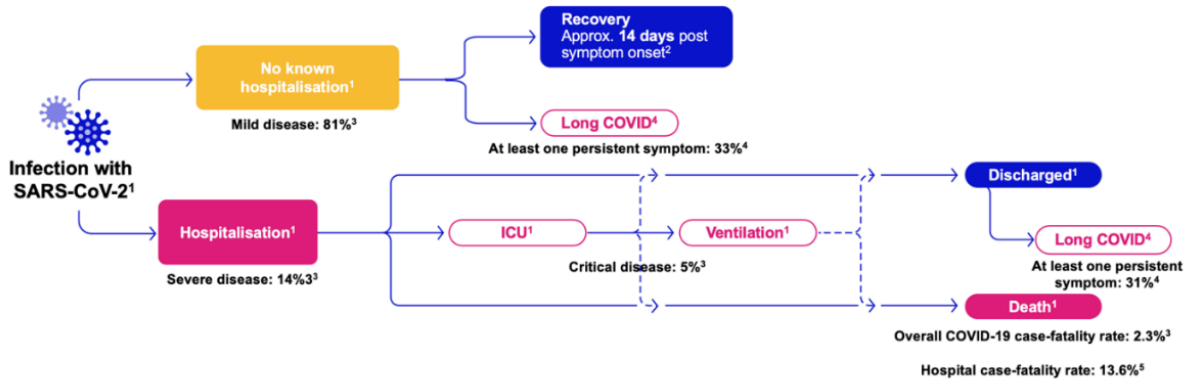


Figure 8: Distribution of COVID-19 cases[14]

This graph gives us an overview of how infections with SARS-CoV-2 are developing during their course. Over 80% of infected persons don't need hospitalisation and recover after 14 days. But still 33% of them develop Long-COVID where at least one symptom persists. Scientific research data shows that 14% of infected persons needed to be hospitalized and 5% had to go to ICU and even needed hospitalisation. At the end 2,3% of the patients died due to COVID-19. That shows how severe the complications can get.

The most common complication is a severe pneumonia which can lead to acute respiratory distress syndrome and later to respiratory failure. About 15% of people with COVID-19 develop serious complications, including COVID-19 pneumonia.[15] It might sometimes be hard to distinguish clinically weather a COVID-19 infection is already a pneumonia or not because the symptoms can be quite similar. One of the major indicators is the decreased breathing capacity.

Compared to normal pneumonias where we have a rapid infection of large regions of the lung, COVID-19 pneumonia sets up in multiple small areas of both lungs. It then causes the immune cells of the lung to spread over a period of days or even weeks. Since the infection slowly moves through the lung, it leaves damage and continuously causes fever, low blood pressure and causes damage to several organs like the kidneys, the brain or the heart. The severe complications of COVID-19 might be related to the long course of disease.[16]

If a COVID-19 pneumonia gets worse, it can lead to an acute respiratory distress syndrome which is a massive inflammatory reaction of the lung followed by an impaired oxygenation of

[14] (Estiri H, 2020)
[15] (Cleveland Clinic, 2023)
[16] (Paul, 2021)

the blood resulting in hypoxemia and pulmonary infiltrations. It is mainly associated with respiratory failure. It is a severe medical condition where the patients, depending on their condition either need non-invasive or invasive ventilation.

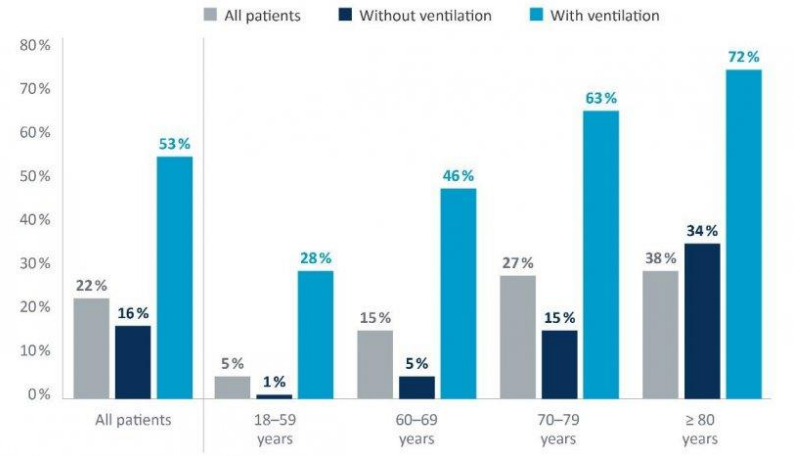


Figure 9: In-hospital mortality of patients with COVID-19 [17]

A study in Germany in 2020 showed that around 20% of COVID-19 patients admitted to the hospitals died. The mortality rate for those patients who were ventilated was 53%. The mortality rate for those without artificial lung ventilation was significantly lower - 16%. During this period, 17% of all patients were ventilated. This shows very clearly how poor the outcome is for people with complications, especially if we look at older patients. The mortality rate for people over 60 years of age was already 46% if they were ventilated. The risk was even higher for patients over 80 years old - 72%.

9. TREATMENT & MANAGEMENT

Treatment options for COVID-19 are depending on the phase of disease and the severity of symptoms. It may include antiviral medications, oxygen support, immunomodulatory therapies, and mechanical ventilation. It is important to individualize the treatment, based on the patient's specific symptoms and medical history. It should be provided under the guidance of a healthcare professional.

To understand the different treatment options, one has to understand the common pathway of the disease. We already heard of the phases of COVID-19 infections. This graph shows the pathophysiological activity of the body during an infection.

[17] (German Interdisciplinary Associationof Critical Careand Emergency Medicine, 2020)

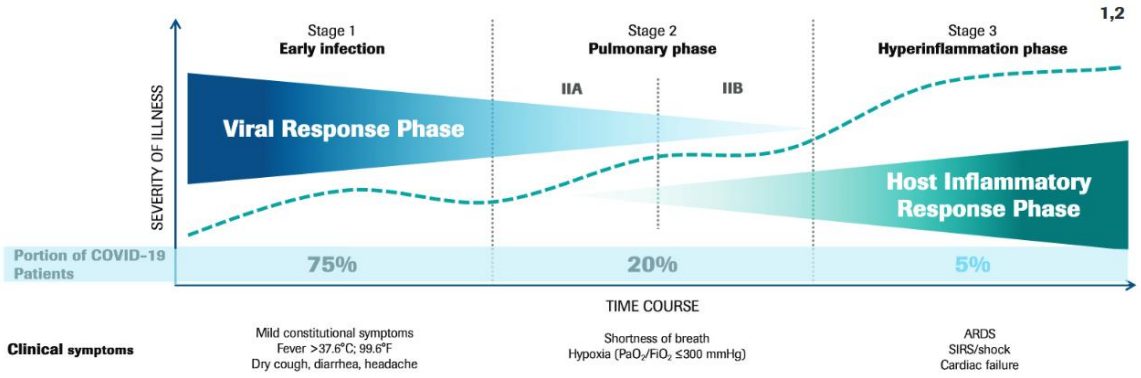


Figure 10: Stages of a COVID-19 infection [18]

In the early beginning of the infection, COVID-19 is driven by the replication of the virus. That means the higher the replication rate, the more severe the infection gets. Patients show mild symptoms like fever or dry cough. After we enter stage 2 also called pulmonary phase where the viral response gets displaced by the inflammatory immune response. Approximately 20% of COVID-19 patients reach this phase showing symptoms like shortness of breath, with or without hypoxia and abnormal chest x-ray.

Later in stage 3, the disease is mainly influenced by the immune response of the patient causing a severe inflammatory response which can lead to tissue damage. Approximately 5% of all COVID-19 patients enter this phase, which leads to ARDS, SIRS or even cardiac failure. This correspondences with elevated inflammatory markers, high troponin or NT-pro BNP elevations.

According to these stages the therapies differ. To fight against the virus in early stages it is important to target the virus itself while immunosuppressive therapies are more efficient in later stages of the disease.

In the treatment guidelines the COVID-19 infection is divided in five categories starting with asymptomatic infections, followed by mild, moderate, severe and critical illness. Before treating a patient, he should be classified to target the therapy. It is also important to differentiate between hospitalized and non-hospitalized patients.

[18] (Roche, 2023)

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients (**AIII**). • The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication (**AIIb**).
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] (**AIIa**) • **Remdesivir**[d,e] (**BIIa**) *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] (**CIIa**)
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.	

Figure 11: Therapeutic management of non-hospitalized patients[19]

This table from US National Institute of Health (NIH) recommendations shows the latest guidelines for the therapeutic management of non-hospitalized patients who are suffering from mild or moderate symptoms and don't need supplemental oxygen. As one can see all patients should be offered symptomatic treatment like antipyretics, analgesics or antitussives. A good hydration is also very important.

Patients with risk for a progressing disease should be treated with ritonavir boosted nirmatrelvir, an oral antiviral pill, which should be started within five days after developing symptoms. Usually, one has to take three pills twice a day for five days. A trial published in the "New England Journal of Medicine" showed that it reduces the risk for hospitalisation and death of unvaccinated people by 89%.[20]

Very important to mention is, that it is also highly efficient against the SARS-CoV-2 omicron variant. As mentioned, it is composed of two different components. Nirmatrelvir inhibits the key enzyme that the virus needs to form functional virus particles. This causes the effect that the virus which is released from the cells is no longer able to enter uninfected cells. Consequently, the infection stops. Ritonavir is used as a booster, to support antiviral medications. That happens by ritonavir shutting down the metabolism of nirmatrelvir in the liver. As a consequence, it remains in the body longer and fights against the virus.

[19] (Health, Coronavirus Disease 2019 (COVID-19), 2023)
[20] (Jennifer Hammond, 2022)

On the graph[21] on the right one can see at that nirmatrelvir blocks the proteolysis of the viral proteins so further RNA replication can´t continue. Nirmatrelvir is an orally bioavailable protease inhibitor that is active against MPRO, a viral protease that plays an essential role in viral replication.

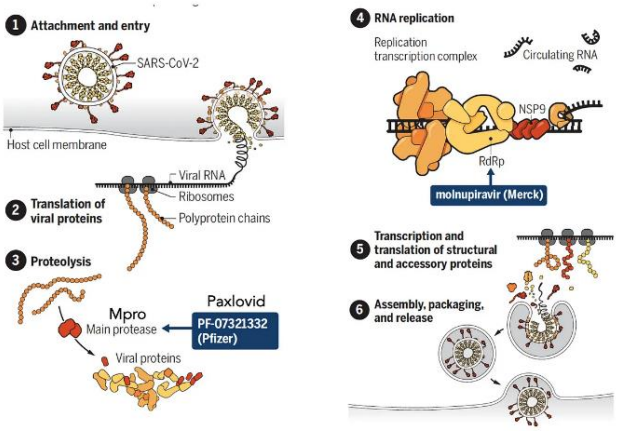


Figure 12: Mechanism of Nirmatrelvir

Side effects of this drug can be drug-drug interactions which cause increased levels of other medications in the blood since ritonavir blocks P450 3A4 and P-glycoprotein. The use of it is also dangerous in patients with severe renal impairment.

Another treatment option is remdesivir which is administered intravenously. It is also recommended for COVID-19 patients.

It is a nucleotide prodrug of an adenosine analogue which binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription. Remdesivir shows good activity against SARS-CoV-2 especially against omicron and its variants. Depending on the severity of symptoms its either given for three or five days.

Systemic corticosteroids (dexamethasone and other corticosteroids) for non-hospitalized patients because of lack of safety and efficacy data are not recommended.[22]

The therapeutic management for hospitalized adults looks quite different to the non-hospitalized. As one can see on the table from NIH recommendations, the therapy is adjusted according to the severity of the disease.

[21] (Ground truths, 2023)
[22] (Peter Horby, 2021)

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

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

Figure 13: Therapeutic management of adults hospitalized for COVID-19 based on disease severity [23]

First, we have patients who are hospitalized with reasons which are not COVID-19 related and they don't need supplemental oxygen. They should be treated according to the guidelines for non-hospitalized patients, which were discussed previously.

Then there are patients who are hospitalized because of COVID-19 but they don't need supplemental oxygen. In this case the guidelines recommend remdesivir as treatment of choice. In this case dexamethasone and other systemic corticosteroids are also not recommended.

For patients who require supplemental oxygen there are different treatment options. Those who require minimal conventional oxygen should be treated as those who don't need oxygen supplementation. Most other patients should as well be treated with remdesivir and dexamethasone. And those who already received dexamethasone and still have rapidly

[23] (Health, Coronavirus Disease 2019 (COVID-19), 2023)

increasing oxygen needs and systemic inflammation, they should add baricitinib per os or tocilizumab intravenously to the persisting medications.

In case patients are hospitalized and require high flow nasal cannula oxygen or non-invasive ventilation one should directly start with dexamethasone plus baricitinib or dexamethasone plus tocilizumab. These are immunomodulators which help to decrease the systemic inflammation and hypoxemia. Additionally, remdesivir should be added.

In the most severe condition, when the patient is already requiring ECMO or mechanical ventilation, we use the same therapy model as for the previous stage with dexamethasone plus baricitinib or dexamethasone plus tocilizumab.

10. COMPARISON OF SARS-CoV-2 MUTATIONS

This following chart, published by the Johns Hopkins University shows course of COVID-19 from the beginning of 2020 until January 2022.

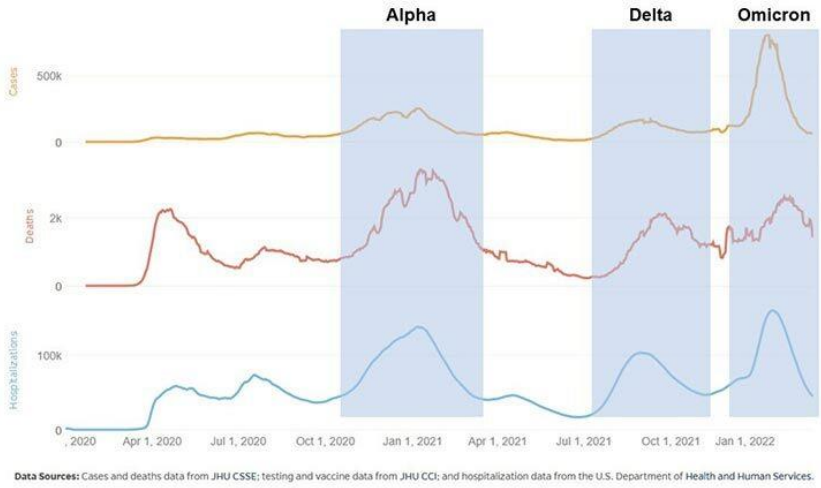


Figure 15: Comparing Cases, Deaths, and Hospitalizations [24]

The data focuses on COVID-19 patients from the United States. The chart is divided in three curves. The yellow one shows the cases of infected people, the red one the death rate and the blue line indicates the hospitalisation rate of people who got infected with COVID-19. The blue frames highlight the major different SARS-CoV-2 mutations during that time.

These statistics point out some significant changes during the pandemic. When the virus started spreading, the relative numbers of cases was quite low compared to later times but even though the numbers were so low, starting in April 2020, there was a drastic rise in the death and

[24] (Blauer, 2023)

hospitalisation rate. The death rate decreased again after one month while the hospitalisation rate kept quite constant over the summer. At that time the disease was completely new and unknown, so first one had to figure out how to manage the patients and how to treat them. No guidelines existed and there was also no vaccine available at that time. Tests needed to be developed to be able to detect the virus. And because of the fast spreading of the virus in many countries the health care systems collapsed, and they were unable to treat all patients. These are some reasons why there were so many deaths reported with the first outbreak of COVID-19 even though the number of infections compared to the following outbreaks with more harmful mutations.

In October 2020 the alpha-mutation was detected, which caused an increase in cases during the whole winter. It was first identified in the United Kingdom and was characterized by increased transmissibility. It was believed to be more contagious than the original strain of the virus. Also, the death rate increased from approximately 1000 deaths in October until almost 3000 deaths in January 2021. At the same time the hospitalisation rate increased from 50 000 to almost 150 000. Until April 2021 the numbers decreased back to the approximate amount where they were before the alpha-mutation started. After that until the end of July they remained quite low. Studies showed that the alpha mutation did spread up to 70% faster [25] from person to person and it also showed a higher mortality[26] then the original variant. This information supports the statistics in the chart. At that time there was still no vaccine available which could prevent severe infections and the spread of the virus. It is important to note that the severity of the disease can vary depending on various factors like healthcare capacity, population demographics, and public health measures in place.

But in the beginning of August 2021 the delta-mutation emerged in India, and it was known for its high transmissibility. In the US it caused less infections, then the alpha-mutation but still the hospitalisation and death rate increased quite high until 100 000 hospitalisations and 2000 deaths daily. The delta variant is between 40% and 60% more transmissible than the previously dominant alpha variant but since vaccinations were already performed the death rate was much lower than it was in the previous alpha wave.

Right after the delta-mutation the omicron-mutation started spreading. It sparked globally concern due to its high number of mutations and caused an increase to over 800.000 cases. But even though the hospitalisation rate was more than three times higher than during the Alpha-

[25] (Erik Volz, 2023)
[26] (Challen, 2023)

wave the hospitalisation rate was around 150.000. And there were also less deaths with Omicron then with Alpha.

During the whole pandemic we saw a relatively stable mortality rate, but it finally changed with the omicron variant, where we had a significant decrease in mortality. This can also be influenced by additional testing capacity but also the symptoms of omicron where less severe than the ones of the other variants. Another reason could be the herd immunity that was reached with the vaccination and previous infection.

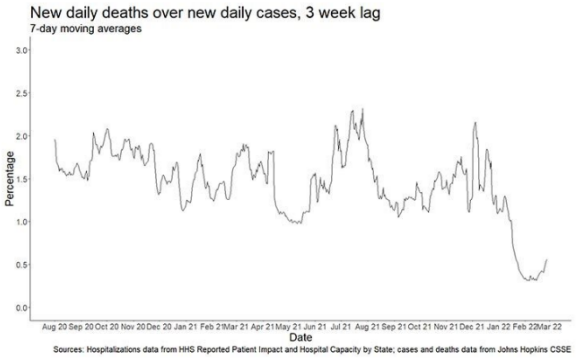


Figure 16: New daily deaths over new daily cases

To sum up, alpha variant had the highest hospitalisation and mortality rate compared to the cases while omicron had a much higher infection rate than the others. But it caused less hospitalisations and deaths. Delta had similar effects than alpha, but it was slightly less harmful.

It was also recognised that the symptoms changed from one variant to another. This chart compares the symptoms of the different mutations. [27]

In the beginning COVID-19 was manifested with fever, persistent cough, fatigue and headache. Only sometimes a sore throat, runny nose or chills were seen. Later, during the time when delta was predominant, it was more common to have a runny nose or sore throat, but fever appeared less often. With omicron persistent cough became less dominant and fever was only seen sometimes, but sneezing became more common.

Frequency of COVID-19 symptoms by variant

SYMPTOM	OMICRON	DELTA	PRE-DELTA
Runny nose	Common	Common	Sometimes
Headache	Common	Common	Common
Fatigue	Common	Common	Common
Sneezing	Common	Sometimes	Rare
Sore throat	Common	Common	Sometimes
Persistent cough	Sometimes	Common	Common
Chills or shivers	Sometimes	Sometimes	Sometimes
Fever	Sometimes	Sometimes	Common

Figure 17: Frequency of COVID-19 symptoms by variant

[27] (ZOE Health Study, 2023)

11. CASE PRESENTATION & ANALYSIS

11.1. THE CASE OF 90 YEARS OLD J.M.

11.1.1. ANAMNESIS

A 90-years old man was treated in the VUH from 28.12.2022 until 12.01.2023 with the diagnosis of COVID-19 with bilateral pneumonia and acute respiratory failure.

Disease Anamnesis:

He suffered from general weakness, dizziness, and shortness of breath. He also complained about episodic chest discomfort related to physical exertion. The symptoms started one day before the admission to the hospital, when he was coughing, had a fever up to 39 degree and a sore throat. He was treated with paracetamol for the fever, but the effect was negligible. As his symptoms worsened, the next day he was hospitalized.

Epidemiological anamnesis:

The patient has had three vaccinations against COVID-19, but has not received the seasonal influenza vaccine in 2022. He stated that he had direct contact with his wife who had previously tested positive for SARS-CoV-2.

Medical history

The patient has a history of hypertensive heart disease, angina pectoris, chronic arterial fibrillation, left ventricular failure, stage 3 chronic kidney disease, hyperuricemia and hypothyroidism.

General medications:

- Apixaban 2.5 mg BID for anticoagulation,
- Bisoprolol 5 mg QD to treat his hypertension,
- Valsartan 24/26 mg BID because of heart failure
- Torasemide up to 20 mg QD a diuretic used to treat fluid overload due to heart failure, kidney disease, and liver disease and high blood pressure

The patient had classical symptoms of a COVID-19 infection. He also suffered from chronic cardiac symptoms, were further complications need to be ruled out. Since he was complaining about shortness of breath and fever, it was mandatory to do further investigations to prevent him from COVID-19 complications. Additionally, we have to take into account, that the patient was at a very advanced age and has several comorbidities affecting the heart and kidneys and thyroid. These can influence the course and outcome of the disease a lot leading to severe complications or even death. Looking at the statistics previously discussed he has a mortality risk of 34%. Because of these circumstances and his continuous dyspnea, it was necessary to hospitalize the patient and not to treat him outpatient.

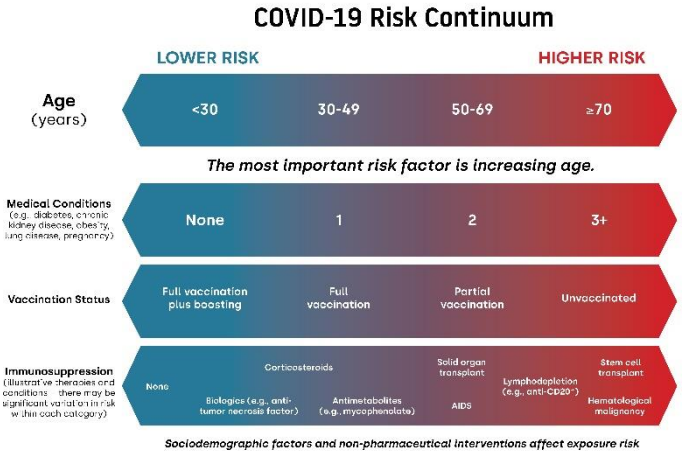


Figure 18: COVID-19 risk evaluation

On this graph[28] we can have a look on the risk factors influencing the outcome of the disease. It shows that the highest risk factor is the increasing age. Since our patient was already at an age of 91, he was definitely very vulnerable. Also, medical conditions like diabetes or chronic kidney diseases increase the risk. Another factor affecting the outcome was the vaccination status, but since the patient was vaccinated against COVID-19 he improved his chances. Other factors can be immunosuppression where he is not affected or sociodemographic circumstances.

11.1.2. CLINICAL EXAMINATION

On clinical examination the patient was afebrile, he was hemodynamically stable with a blood pressure of 101/60. His heart rate was 80 bpm. On auscultation vesicular breathing sounds were heard with basal crackles. Oxygen saturation without supplemental oxygen was 85%. The saturation improved after giving 4 l/min oxygen via nasal cannulas to SpO2 95%. The patient´s abdomen was soft and painless. There were no edemas found in the legs.

The clinical examination ruled out the fever and blood pressure and pulse are in the range, but his oxygen saturation was 85% which showed that the lungs were already impaired by the infection and also the crackles gave us the assumption of a pneumonia. As mentioned before,

[28] (COVID-19 REAL TIME LEARNING SYSTEM, 2023)

pneumonia is one of the most common complications and can lead to further even more severe complications, that's why it is important to start with the treatment as soon as possible.

11.1.3. CLINICAL INVESTIGATIONS

Laboratory testing was performed. The most important values and their development can be seen in the table below.

	Norm	**28.12.**	**30.12.**	**02.01.**	**04.01.**	**07.01.**	**10.01.**
CRP (mg/l)	0-5	204,5	161	42.6	86,9	20,2	28,7
Procalcitonin (µg/l)	0,1-0,25	1,22			0,19		
WBC (*10^9/l)	4,5-11	13,23	14,07	11,49	8,59	8,92	6,4
Neutrophils (%)	54-62%		89,8	86,4	86	83,1	63,9
Lymphocytes (%)	25-45%		4,7	5,2	6	8,1	21,8
AST (U/L)	8-33	28	31				
ALT (U/L)	4-36	19	23				
Creatinin (µmol/l)	62-114	186	173	139	125	107	110
Troponin (ng/l**)**	<0,4	120,7 239	170				
PLT (*10^9/l)	140-350	200	148	269	261	255	201
MCV (fl)	85-95	101	99.6	100.4	100,1	100,2	99,5
HB (g/dl)	13,5-17		11,5	11,9	11,0	11,4	11,1
Lactate (mmol/l)	0,5-2,2				1,0		1,0
Glucose (mmol/l)	7-4	6,3			7,2		5,9

PCR-test for SARS-CoV-2 RNA was positive (CT-value of 20,3).

Primary blood count showed neutrophilic leukocytosis, lymphopenia and moderate macrocytic hyperchromic anemia. The electrolytes were in normal range (K (mmol/l): 4.9, Na (mmol/l): 138, Cl (mmol/l): 109,).

The clinical investigations confirmed the diagnosis of COVID-19 infection with a positive PCR-test. Additionally, the inflammatory markers including CRP and procalcitonin showed significant elevation. CRP (mg/l): 204.5, Procalcitonin (µg/l): 1.22.

And also, the WBC showed a neutrophilic leukocytosis, that means that we already had an immunological response to the virus and is a classic sign of an infection.

As one can see all these inflammatory markers decreased during Patient J.M. hospitalization period. On the day of discharge, the CRP had decreased to 28,7 mg/l and the WBC was back in the norm 6,4 *10^9/l.

Liver and kidney function were also monitored and while liver function was always in the range (ALT (U/l): 19, AST (U/l): 28), the creatinine was elevated in the beginning (creatinine 186 µmol/l) but also improved over the time (creatinine 110 µmol/l).

The cardiac markers were highly elevated showing a NT-pro BNP 3526 ng/l and Troponin I of 120.7 ng/l (19:15) which even increased to 239.0 ng/l (20:55). Because of the increased Troponin levels a cardiologist was consulted. Since the patient showed symptoms of angina pectoris a myocardial infarction must be ruled out immediately. But there was no clear evidence for an acute coronary syndrome also because the ECG didn't show any signs for acute ischemia. The elevated troponin was expected to be from a secondary pathology, an infection and the chronic kidney disease.

The x-ray showed signs of infiltrations in both lungs. These could already be expected after the auscultation and can now confirm our diagnosis of pneumonia.

11.1.4. PROCEDURE & THERAPY

On day of hospitalization empiric antimicrobial treatment was started with Amoxicillin/ Clavulanic Acid 1200mg. Since there was a risk for bacterial co-infections together with COVID-19 infections and an even higher risk for secondary infections during hospitalization, antibiotic therapy can be started in these cases.[29] Symptomatic therapy was started with ringer solution 500ml preventing dehydration and paracetamol 1000mg for pain and fever management.

As we saw in the guidelines, COVID-19 patients are categorized according to the severity. In this case, he was treated according to level 3, since his SpO2 was primarily at 85% and he needed oxygen therapy. Primarily, he was treated symptomatically but treatment with remdesivir and dexamethasone was started as well according to the national institute of health (NIH) guidelines. Additional options would have been baricitinib or tocilizumab which could be given on top for example if the therapy wouldn't have shown any success. He continued taking Apixaban and got Nadroparin additionally for anticoagulation because of increases risk for thrombosis. If patients are not anticoagulated it is important to start with a prophylactic dose

[29] (Tat Ming Ng, 2022)

of heparin. Captopril, metoprolol and entresto were taken to regulate the blood pressure, pulse and cardiac deficiency.

On 2nd of January a second x-ray was performed which showed reduced infiltrations bilaterally in the peripheral parts. That submitted that the therapy caused regressive symptomatic.

An additional ECG showed chronic atrial fibrillation without signs of acute ischemia.

During his recovery phase he still showed shortness of breath, weakness and poor exercise tolerance remains. In the case of a stable condition, he was discharged for further outpatient treatment and started rehabilitation stage II for 20 days, which means return/improvement of independence, movement functions, psychological state correction, solving social problems and increasing physical exertion tolerance.

11.1.5. SUMMARY

The goal of the hospitalization was to prevent complications, maintain and improve existing functional conditions, compensate impaired functions, improve the myocardial function as well as the respiratory functions.

The patient was hospitalized due to bilateral pneumonia and high inflammatory indicators. Empiric antibacterial treatment was started, and the viral pneumonia was monitored. During the treatment the conditions improved, his respiratory impairment almost resolved. The minimum oxygen requirement remains ~2 l/min and he still had poor exercise tolerance. In the case of a stable condition, he was discharged for further outpatient treatment and rehabilitation.

During his hospitalization period the patient was treated with following medications:

- Amoxicillin and clavulanic acid; mg; injection/inf. solution, 1200 mg, TID. (10 days)
- Apixaban; mg; tab., 2.5 mg, BID.
- Captopril; mg; tab., 25 mg QD,
- Dexamethasone; mg; injection/inf. solution, 8 mg QD, 10 days
- Electrolyte (Ringer); ml; injection/inf. solution, 500 ml,
- Furosemide; mg; injection/inf. solution, 60-40 mg,
- Metoprolol succinate; mg; tab., 23.75 mg,
- NaCl 0.9%; ml; injection/inf. solution, 1000 ml,
- Nadroparin calcium; ml; injection 0.3 ml BID. -> 0.6 ml BID.
- Omeprazole; mg; tab., 20 mg QD,
- Remdesivir; mg/ml; injection/inf. solution, 200 mg/ml QD,

- Remdesivir; mg/ml; injection/inf. soln., 100 mg/ml QD, (4d)
- Sacubitril et Valsartan; tab., 50 mg, information: Entresto 24/26mg BID.

The patient was discharged with stable vital signs and general appearance. He got a recommendation for outpatient care, control and supervision of his family doctor. Leukocytes, CRP and Creatinine should be controlled routinely after 7 days, and a chest x-ray performed after 1 month. He should also consult a pulmonologist. Rehabilitation should be continued.

Medications should be continued as followed:

- Sacubitril, Valsartan 24/26 mg BID.
- Apixaban 5mg BID. (following indicators of kidney function, in the presence of creatinine >133mmol/l, reduce the dose to 2.5mg BID)
- Bisoprolol 5mg QD

This therapy showed great success and his symptoms improved. But one can say that at the time of discharge he still suffered from decreased exercise tolerance. People hospitalized with COVID-19 often need weeks to months to fully recover from the infections due to possible long-COVID or post-COVID syndrome. It is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 infection. It includes a big range of health problems which last further after the actual infection. It mostly occurs in people who previously had severe symptoms or who were not vaccinated.[30]

11.2. THE CASE OF 73 YEARS OLD S.S.

11.2.1. ANAMESIS

73-year-old man was treated in the VUH from 04.01.2023 until 02.01.2023 with the diagnosis of COVID-19 infection and bilateral bacterial pneumonia.

Disease anamnesis:

Patient was complaining about general weakness, shortness of breath, febrile fever and cough. His symptoms started 10 days before admission to the hospital and he also got tested positive for SARS-CoV-2 at that time. The patient got outpatient treatment. Since his symptoms got worse at home, he was hospitalized.

[30] (Centers for disease control and prevention, 2022)

Medical history

The patient has a history of type 2 diabetes mellitus and diabetic polyneuropathy. Hypertensive heart disease without congestive heart failure and unspecified chronic kidney disease. The patient denies any allergy.

Medications

- Lorsartan Lercanidipine 10mg QD for regulation of the blood pressure.
- Gliclazide 60 mg QD to control type 2 diabetes mellitus.
- Metformin hydrochloride 750 mg after 2 tablets QD to control his type 2 diabetes mellitus
- Silymarin

As in the previous case, patient S.S. presented with several risk factors for developing complications or severe outcome. He was at older age and suffered from various comorbidities like type 2 diabetes mellitus or a chronic kidney disease. The patient was primarily treated at home, which is good as long as he doesn't experience more severe symptoms like for example breathlessness. Getting hospitalized always comes along with a higher risk of getting a nosocomial infection.

11.2.2. CLINICAL EXAMINATION

During status assessment he appeared haemodynamically stable (128/74), no fever (36,5 °C), heart rate 89bpm and SpO2 96% with supplemented oxygen 3 l/min. Abdomen was soft, no signs of peripheral oedema. Patient needed supplementary oxygen to maintain a high saturation concentration, as shortness of breath would otherwise cause hypoxia.

11.2.3. CLINICAL INVESTIGATIONS

Laboratory testing was performed. The most important values and their development can be seen in the table below.

	Norm	**04.01.**	**06.01**	**08.01. ICU**	**11.01. ICU**	**18.01. ICU**	**24.01. ICU**	**01.02.**
Troponin (ng/l**)**	<0,4	17,4						
NT-pro BNP				457		127		
Creatinin (µmol/l)	62-114	121	99	90	92	78	93	107
CRP (mg/l)	0-5	389	311,7	329,4	362	34,9	51	13,5

Procalcitonin (µg/l)	0,1-0,25	0,67	0,38	0,16	0,35		0,04	
Glucose	4-36	11,59	11,6	8,06	10	14,0	9,9	
AST (U/L)	8-33	39			29			
ALT (U/L)	4-36	14			12			
WBC (*10^9/l)	4,5-11	9,03	10,12	10,43	12,92	11,57	9,59	8,3
Lactate	0,5-2,2		2	1,35	1,53	1,42	1,3	
Hb (g/dl)	13,5-17		10,2	11,0	99	10,0	12,0	11,0
PLT (*10^9/l)	140-350		361	426	391	358	278	255

The results of the PCR test showed that Influenza virus A & B as well as RSV were negative while SARS-CoV-2 showed a positive result.

At admission the patient showed very high inflammatory markers with CRP of 387.9 mg/l and procalcitonin 0.67 µg/l. Leukocytes were in the range. He also showed elevated troponin levels and slightly elevated creatinine, which could also be due to his chronic kidney disease. The patient also showed an anaemia with haemoglobin of 10,2 g/dl. A study in 2021 showed that, 61% of participants who all suffered from a COVID-19 infection also presented with an anaemia. So, an anaemia is quite commonly associated with COVID-19. But it is very important to know that it is not associated with a higher mortality rate. [31] The anaemia remained over his whole time of hospitalisation.

In further investigations, blood cultures were taken because of his signs of infection. The urine test didn't show any bacterial growth or any other pathologies.

On 4th of January the chest x-ray showed massive polysegmental infiltrations of both lungs which lead to the conclusion of a reciprocal viral pneumonia. Four days later a new x-ray showed significantly negative dynamics. The airiness of the lungs were significantly reduced. On both sides of the lungs, in all lobes, pronounced, converging dimming's was observed. His clinical status worsened so that he needed to be transfered on the ICU. The inflammatory markers were also still very high with rising WBC and CRP of 329 mg/l.

He remained on the ICU for 16 days, primarily with persisting high inflammatory markers, elevated CRP, procalcitonin. Also, NT-pro BNP was elevated, indicating myocardial impairment. Only after ten days on 18th of January, his blood tests showed better results with

[31] (Gaetano Bergamaschi, 2021)

a CRP decreased to 34,9 mg/l and procalcitonin of 0,04 µg/l. The other pathological values all, developed back to the normal range, showing decreasing NT-pro BNP, WBC, lactate and creatinine.

More x-rays were performed on 11th, 16th, 23rd, 24th showing weakly positive dynamics with decreasing infiltrations.

After he was transferred from the ICU to the COVID-19 department on 24th of January his blood test constantly improved further so that he could be discharged on 1st of February with a CRP of 13,5 mg/l and WBC of 8,3 *10^9/l.

11.2.4. PROCEDURE & THERAPY

At the beginning of hospitalization, the patient had an increased oxygen demand with up to 15 l/min with low oxygen saturation and physical exertions.

As in the first case he was treated symptomatically and a therapy with remdesivir for 5 days was started because he was categorized similarly. Additionally, an empiric antibiotic therapy was started with Amoxicillin and clavulanic acid; mg; injection/inf. solution, 1200 mg, TID for 7 days and 4 g piperacillin and 0.5 g tazobactam TID for 8 days. Electrolytes correction was started because of a volume imbalance. Further investigations were thrombosis and stress ulcers prevention and treatment of chronic diseases. Of course, his chronic diseases like diabetes mellitus and hypertension were also continuously treated.

When he was transferred to the ICU on 08.01.2023 because of worsening status, oxygen therapy with NIV alternating with Hi-Flow through a leaky mask was started. In the mean while the patient developed a delirium which was controlled with antipsychotic drugs. Antibiotic treatment was continued with Amoxicillin and clavulanic acid and piperacillin and tazobactam were continued until 19.01.2023.

Correction of electrolyte imbalance and volemia, the prevention of thrombosis and stress ulcers and the treatment of chronic diseases was continued.

After clinical improvement and stabilization, on 24th of January he was transferred to the COVID-19 department where he remained until 01.02.2023. The chest x-rays were repeated to document the course of the pneumonia and it showed positive dynamics in the lungs with decreasing infiltrates.

In the urine sample on 26.01.2023 was a clinically significant growth of *Klebsiella pneumoniae*. Therefore, a treatment with Sulfamethoxazol/Trimethoprim 960mg started. Patient's condition improved so that the need for additional oxygen decreased to 2-3 l/min.

At that time, he was treated for diabetes, anticoagulation, hypertension, ulcers and quetiapine.

On the day of discharge, the patient condition was good. He was conscious and oriented and mobile. His temperature was 36.2 °C. He was hemodynamically stable with a BP 140/70 mmHg, HR 80 rpm. The SpO2 ~87% without oxygen, and 95% with O2 2.5 l/min via leaky mask. Under these conditions the patient was able to continue his recovery at home.

11.2.5. SUMMARY

Summarizing we can say that patient S.S. was hospitalized due to a COVID-19 infection with progressing dyspnea due to a pneumonia. During his hospitalization the symptoms worsened so that he had to be transferred to the ICU, but there he was able to improve so that he could be transferred back to the COVID department and later discharged. He additionally developed a urinary tract infection and a delirium during that period.

After discharge the patient was supported by a family doctor and pulmonologist.

His medications were continued as followed:

- Acetylcystein 600 mg QD to improve expectoration as needed
- Amlodipine 5 mg QD in the morning
- Metoprolol succinate 47.5 mg QD in the morning
- Omeprazol 20 mg QD
- Gliclazide 60mg QD
- Metformin hydrochloride 750 mg QD
- Quetiapin 50 mg QD

It this case it was not mentioned weather the patient was vaccinated or not, but the newest data confirms again how important it is to be vaccinated against COVID-19. [32] This graph shows the death rate of people in the United States, comparing vaccinated and not vaccinated. The graph shows the course from October 2021 until March 2023. The orange line marks the death rate of unvaccinated people while the purple one shows the one of vaccinated people. The difference is clearly visible here. In winter 2021 the mortality rate was at around 33 while for vaccinated it was only three. That means its approximately ten times higher for unvaccinated people. And even though the overall death rate decreased, the ratio is still the same. This is a very clear indicator for the advantage of vaccinations, not only regarding the mortality rate but also for preventing severe outcomes.

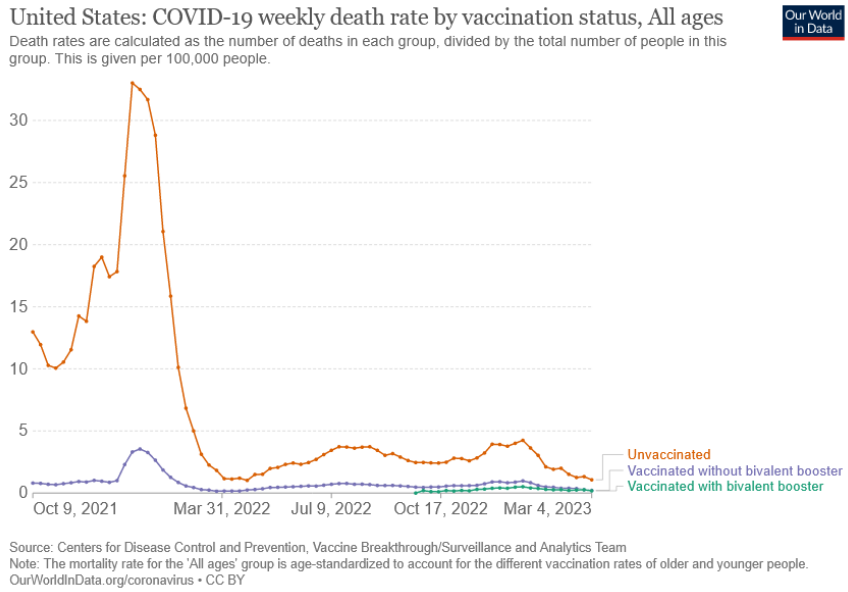


Figure 19: Frequency of COVID-19 symptoms by variant

12. CONCLUSION & RECOMMENDATIONS

Summarizing we can say that COVID-19 can result in a wide range of clinical presentations. It can vary from an asymptomatic or mild disease to severe illness which can lead to respiratory failure and multiple organ dysfunction. There are several different risk factors which have been identified and can cause severe diseases. These include advanced age, obesity, diabetes and cardiovascular disease. Additionally, some populations, such as racial and ethnic minorities and those with lower socioeconomic status, may be disproportionately affected. These disparities may be related to underlying comorbidities, social determinants of health, and access to healthcare.

Over the course of the pandemic several treatment options for COVID-19 have evolved. So, right now the health care system is able to treat patents very efficiently and much better than at the beginning of the pandemic, but difficult cases can still present challenges for healthcare

[32] (Centers for Disease Control and Prevention, 2023)

providers. Also, with the start of the vaccinations, the risk for severe courses of the disease could be significantly decreased. Nevertheless, it is still very important to continue research and collaboration. This includes further investigation into the pathophysiology of the disease, the development of new therapies, and efforts to address healthcare disparities that contribute to poorer outcomes in some populations. It is crucial that healthcare providers, researchers, and industry partners can help to identify new therapies and treatment approaches. This will be essential in improving outcomes for difficult cases of COVID-19.

It is important that healthcare providers should be aware of the risk factors for severe disease and monitor high-risk patients closely. Vulnerable patients must be detected as soon as possible to be able to start a quick therapy and prevent severe outcomes.

Efforts should be made to address healthcare disparities and improve access to care because all patients need to have equal access to treatment. The healthcare system should try to create more attention on the topic, so people get more awareness. For example, public health messaging should emphasize the importance of vaccination and other preventive measures, such as mask-wearing and physical distancing, to prevent the spread of COVID-19 and reduce the burden on healthcare systems.

As we see, that so many people suffer from long-COVID which means they suffer from symptoms for a very long time, long-term monitoring and care for COVID-19 survivors should be a priority as well. With these information’s given the potential for long-term sequelae and complications can be analysed and eventually be decreased.

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