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The long lasting symptoms of the COVID-19 pandemic

A literature research on the persisting symptoms of COVID-19 patients

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Bachelor Thesis Biomedical Sciences
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Foreword

The pandemic caused by the outbreak of SARS-CoV-2 has affected the daily life of many people. I have, personally, not been able to visit any physical courses since the first measures taken against COVID-19 in april 2020. This, together with an increased interest in lung diseases after a research project about COPD supervised by prof. Dr. Reinoud Gosens, has led to a bachelor thesis surrounding the topic of COVID-19.

Summary

COVID-19 has heavily affected almost all countries in the world. It has already been around for more than 18 months since the first discovery in Wuhan, China in late 2019 and it has infected more than 175 million people and is accountable for almost 4 million victims worldwide. Persistent symptoms related to COVID-19 are commonly seen in people that recovered from the SARS-CoV-2 infection and can vary significantly between individuals, similar to the symptoms experienced during the acute phase of COVID-19. Early data from hospitalized people showed a common seen characteristic in these individuals with severe COVID-19, this commonly seen characteristic are comorbidities. Lung transcriptome data from people with comorbidities like chronic obstructive pulmonary disease and hypertrophy, often seen together in patients with severe COVID-19, showed an significant increase in ACE2 expression, the crucial host receptor for SARS-CoV-2 binding and entry. This suggests that people with comorbidities have an increased chance of developing a more severe COVID-19. Another study showed that people with comorbidities, and a high symptom load during acute COVID-19, are associated with an increased chance of developing long lasting COVID-19 related symptoms. Also, some people with severe COVID-19 are treated similar to people with ARDS, this might cause additional pulmonary damage in some individuals and worsen the rehabilitation, as some develop an atypical form of ARDS. Understanding which people in the population are vulnerable to COVID-19 helps to develop strategies to protect them and decrease the societal damage caused by SARS-CoV-2 or a potential future viral outbreak.

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Introduction

The COVID-19 pandemic is impacting everyday life in almost every country in the world, even though it has been around for more than a year. The pandemic has heavily backlogged public healthcare as the main focus is on containing the spread of the virus. This has resulted in many delayed medical operations and people with undiscovered illnesses. The number of global cases already exceeds 175 million as of the 15th of june 2021 and millions of new COVID-19 cases are added to this every week. However, vaccination programmes show to be effective in battling the COVID-19 pandemic as the daily cases are decreasing significantly in countries with a high rate of vaccinated people. The weekly case incidence is the lowest since February 2021 with a decline in the amount of weekly cases in all WHO (World Health Organization) Regions, except for Africa (*Weekly Epidemiological Update on COVID-19 - 15 June 2021*, z.d.). Figure 1 shows an optimistic decline in the number of COVID-19 cases and deaths on a global scale, but it is far from being resolved. There are still uncertainties about the effectiveness of the vaccines in the long term and on future variants of SARS-CoV-2, as coronaviruses frequently undergo recombination of their genome (Su et al., 2016). The BNT162b2 vaccine of Pfizer-BioNTech already showed to be less effective in protecting against the B.1.351 variant of SARS-CoV-2 than the claimed effectiveness claimed by the clinical trials (Abu-Raddad et al., 2021). Furthermore, the delta variant of the virus (B.1.617.2), which was initially detected in India, is already the dominant variant that is circulating in the United Kingdom (Torjesen, 2021).

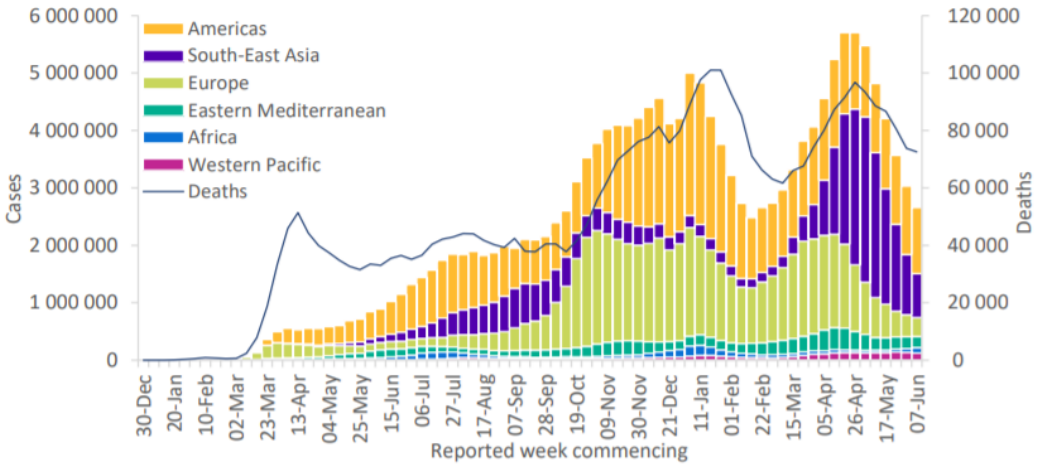

Figure 1. Weekly COVID-19 cases and deaths reported by WHO Regions. (Weekly Epidemiological Update on COVID-19 - 15 June 2021, z.d.)

1.1 SARS-CoV-2

COVID-19 (Coronavirus Disease 2019) is the name for the disease caused by the infection with SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). The virus is mostly transmitted through touch and aerosols and it is thought to originate from bats and transmitted to humans via a mechanism called zoonoses (Corman et al., 2018). Coronaviruses, like

SARS-CoV-2, are single-stranded positive-sense RNA viruses that are able to infect animals and humans and can cause respiratory, gastrointestinal, neurological and hepatic diseases (Weiss & Leibowitz, 2011). The mechanism of binding and entering target cells of humans and other animals is mediated by the spike glycoprotein (S protein) of the enveloped coronaviruses (Gallagher & Buchmeier, 2001). Together with the expression of membrane protein ACE2 (angiotensin-converting enzyme 2) on human cells, they are required for the binding and entering of SARS-CoV-2. The S protein is primed by host cell serine protease TMPRSS2 (transmembrane serine protease 2) upon binding to the ACE2 receptor (Hoffmann et al., 2020), which is essential for the viral spread between the host's target cells (Iwata-Yoshikawa et al., 2019). ACE2 and TMPRSS2 are co-expressed in lung type II pneumocytes, nasal goblet secretory cells and ileal absorptive enterocytes, which may explain the rapid spread of SARS-CoV-2 and damage caused in the lung epithelium (Ziegler et al., 2020).

Clathrin mediated endocytosis is triggered after the interactions between the spike protein of SARS-CoV-2 and the ACE2 receptor (Bayati et al., 2021). The virus is taken up by the cell and transported via the vesicular system, from early endosomes to late endosomes. The endosome transports to the perinuclear region, whilst dropping in pH and gradually routing towards a degradative lysosome. Finally, the endolysosomal membrane and viral envelope will fuse to create a pore in the endosomal membrane, allowing the release of the viral RNA into the cytosol of the host cell and preventing it to be degraded inside the lysosome (Mercer et al., 2010). The genome RNA of SARS-CoV-2 is replicated in the cytoplasm, inside of cytoplasmic replication factories. The genome is expressed, then assembled into virus particles, which are subsequently released outside of the host cell and are able to spread to other host cells or hosts (Denison, 2008).

1.2 Pathophysiology of acute COVID-19

The symptoms seen in COVID-19 patients may vary significantly per person. Most individuals experience COVID-19 with symptoms that are comparable with symptoms of the flu, like a sore throat and headache, whilst some people are even asymptotic and don't have any notable symptoms. Anosmia and dysgeusia, the loss of smell and the loss of taste respectively, together with fever, cough, fatigue and shortness of breath are common and non-specific symptoms of COVID-19 (Klopfenstein et al., 2020). However, the SARS-CoV-2 infection can cause more severe pneumonia and even respiratory failure in some individuals, the damage caused to the lungs is the lethal factor in the majority of the COVID-19 patients (Bösmüller et al., 2021).

Post-mortem examinations have shown histologic patterns in COVID-19 lung injury. Diffuse alveolar damage (DAD) is the main pattern and is part of acute respiratory distress syndrome (ARDS). Diffuse alveolar damage is a type of acute lung injury (ALI) with defined stages which starts off with early pulmonary edema (retention of fluids). This is followed by damage to epithelial and vascular tissue, which results in necrosis of epithelial cells, inflammation and exudation of proteins originating from blood. The exudations of proteins can be described as hyaline membranes (Borczuk, 2021). The post mortem examinations showed that diffuse alveolar damage was often combined with severe capillary congestion, thrombosis of small to

medium sized arteries and pulmonary embolism. This suggests the presence of vascular dysfunction in the lungs and causing impaired pulmonary blood flow, ultimately leading to severe hypoxemia (low level of oxygen in the blood) (Gattinoni, Chiumello, et al., 2020; Menter et al., 2020). Finally, there is a subacute phase with fibroblastic proliferation and hyperplasia of type II pneumocytes (Cardinal-Fernández et al., 2017). The fibroblastic proliferation may lead to a fibrotic lung with patients that experience a longer disease course (Borczuk, 2021).

Other predominant pathophysiologic mechanisms seen in acute COVID-19 are direct viral toxicity, microvascular injury and immune system dysregulation resulting in the stimulation of a hyper inflammatory state . A hyper inflammatory response to battle the SARS-CoV-2 infection is able to cause significant inflammatory damage to tissue of the lung and other organs, worsening the outcome of the infection (Gupta et al., 2020). Severe cases of COVID-19 are characterized by a high viral load with an enormous secretion of inflammatory cytokines in the early stages. The viral load and the level of inflammatory cytokines tend to decrease as tissue repair starts in the later stages of the disease (Bösmüller et al., 2021).

1.3 Persistence of symptoms

The persistence of symptoms after the acute phase of COVID-19 are mentioned more often as more people recover from a SARS-CoV-2 infection. The main focus was on the understanding of the acute phase of COVID-19 and data from people that recovered from COVID-19 was lacking. Most data that is collected at this point is from patients that are hospitalized and monitored by medical specialists. The people that are hospitalized experience a far more severe form COVID-19 than the majority of people and need longer to medically rehabilitate from the damage caused by the viral infection and other complications. 62,5 percent of a group of hospitalized people experienced persistent symptoms at a follow-up visit 50 days after being discharged from the hospital, with 28 percent showing two or more persistent symptoms (Rosales-Castillo et al., 2021). The most common persistent symptoms shown by multiple different small studies are dyspnoea (shortness of breath) and asthenia (weakness and feeling fatigue) (Carfì et al., 2020; Rosales-Castillo et al., 2021).

Persistent symptoms are also seen in non-hospitalized individuals. The percentage of non-hospitalized people that experience persistent symptoms of COVID-19 is significantly lower than in hospitalized individuals, however some do experience symptoms as long as 6 months after COVID-19 onset (Stavem et al., 2021). Figure 2 shows the most common symptoms at the acute phase of COVID-19 and the persistent symptoms 1,5 to 6 months after onset of the disease.

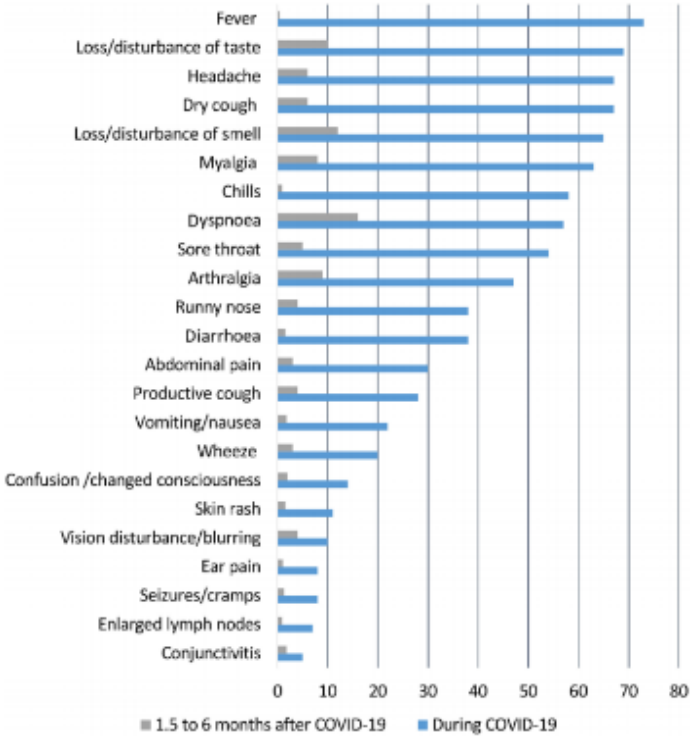

Figure 2. Symptoms experienced during acute COVID-19 and 1,5 to 6 months after acute COVID-19 in non-hospitalized individuals (Stavem et al., 2021).

It is not fully understood why some people experience such long lasting symptoms after COVID-19 and others none. Population based cohort studies are not common enough to gain much data from the majority of SARS-CoV-2 infected people, as most data is currently collected from hospitalized people with severe forms of COVID-19. However, individuals with a mild form of COVID-19 are still able to develop persistent symptoms. The severity of acute COVID-19 is also very variable, with one individual experiencing no symptoms and another developing life threatening pneumonia. The uncertainties around COVID-19 and the persistence of symptoms resulted in the following research questions:

What causes the vast differences in severity of acute COVID-19 between individuals and how is it related to the persistence of COVID-19 symptoms?

How can we improve the outcome of COVID-19 on individual level and population level?

Research findings

2.1 Disease severity

The severity of COVID-19 is highly variable from person to person. Most individuals experience a SARS-CoV-2 infection with symptoms that are similar to those of the flu. However, some are hospitalized after experiencing severe pneumonia that is life threatening or even fatal. Recent studies are trying to understand what is causing severe COVID-19 in those individuals and how treatment can improve a patient's outcome.

It became clear, already in the early stages of the pandemic, that a high percentage of hospitalized people have comorbidities. Two studies, both conducted in january 2020, looked into hospitalized COVID-19 patients in different hospitals in Wuhan, China. Zhou et al., 2020 included 191 total patients with 135 patients from Jinyintan Hospital and 56 patients from Wuhan Pulmonary Hospital, Chen et al., 2020 included 99 patients also from the Jinyintan Hospital. Both studies found that around 50 percent of the COVID-19 patients in those hospitals had an existing comorbidity and the majority were male with a mean age of 55.5 years (Chen et al., 2020). The most common comorbidities are chronic obstructive pulmonary disease, diabetes, hypertension and coronary heart disease, which were all more common in severe cases COVID-19 compared to non severe cases of COVID-19 (Guan et al., 2020).

Pinto et al., 2020 investigated what genes are associated with the increased severity of COVID-19 in people with comorbidities compared to SARS-CoV-2 infected people without existing comorbidities. They started off by looking for lung transcriptome datasets from Gene Expression Omnibus (GEO) which were related to pulmonary arterial hypertension, chronic obstructive pulmonary disease and smoking. This resulted in the identification of seven studies with lung transcriptome data of patients, of which three studies of pulmonary arterial hypertension, three studies of chronic obstructive pulmonary disease and one study with volunteers that smoke compared to non-smoking volunteers.

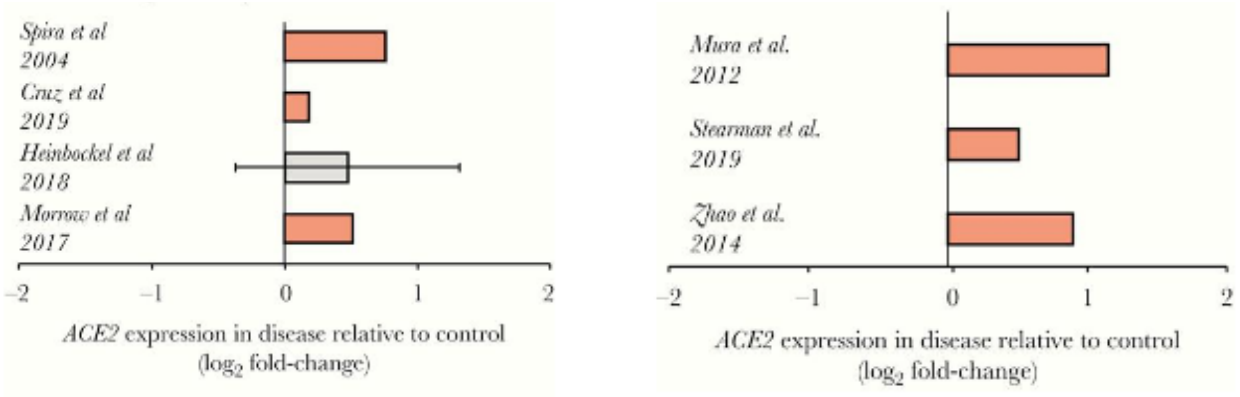

Figure 3. Smoking patients (left) and patients with existing morbidities such as chronic obstructive pulmonary disease (left) and pulmonary arterial hypertension (right) show significant ACE2 upregulation ,compared to their controls, in 6 of the 7 lung transcriptome studies (Pinto et al., 2020).

Differential expression analysis was performed on the data of the 7 studies, identifying 1740 upregulated genes and 938 downregulated genes in the disease group. Enrichment analysis of the differentially expressed genes showed multiple associated pathways, with one upregulated pathway being the ‘viral life cycle’. This pathway describes the mechanisms used by viruses to attach and enter and survive in the host cells. ACE2, together with 25 other genes, is included in this upregulated pathway and is significantly upregulated in six of the seven studies (Figure 2). ACE2 and TMPRSS2 are, the receptor and coreceptor respectively, responsible for efficient SARS-CoV-2 binding and are co-expressed in airway cells like lung type II pneumocytes and nasal goblet secretory cells (Hoffmann et al., 2020; Iwata-Yoshikawa et al., 2019; Ziegler et al., 2020). However, TMPRSS2 was expressed in the lung transcriptome of the 7 studies, but TMPRSS2 was not differentially expressed (Pinto et al., 2020). This suggests that the upregulation of ACE2 in people with comorbidities is worsening the viral infection of SARS-CoV-2, thus leading to more severe cases of COVID-19.

2.2 COVID-19 persisting symptoms

The symptoms experienced by patients after COVID-19 may vary, just like the symptoms during COVID-19, from person to person. Only 12.6% of the patients from one study were free of COVID-19 related symptoms 60 days after onset of COVID-19, with 32 percent still having one or two symptoms and as much as 55 percent with 3 or more symptoms. Many of these patients reported persistent symptoms like asthenia (weakness and feeling fatigue), dyspnoea (shortness of breath) and joint and chest pain (Carfì et al., 2020). However, all these individuals were hospitalized and 72.7 percent were suffering from interstitial pneumonia, not including people with milder forms of COVID-19.

A study was set up by Stavem et al., 2021 assesses the persistence of symptoms in non-hospitalized individuals. They invited 938 subjects in the region of two Norwegian hospitals that were older than 18 years old and identified PCR SARS-CoV-2 positive. People that were admitted to hospital within 21 days after a positive PCR test were excluded, as it was assumed that it was COVID-19 related. This resulted in the response of 451 subjects that provided study information via a survey, in which was asked to fill in a checklist of 21 comorbidities, and a checklist of 23 symptoms during acute COVID-19 and at the time of the survey, about 1.5 to 6 months after the positive PCR test for SARS-CoV-2. The responses were statistically analyzed and a model was created including the dependent variable with the number of the 23 symptoms experienced at the time of the survey and the independent variables; categories of the number of comorbidities (0, 1, 2, or >3), number of symptoms experienced during acute COVID-19 (0-5, 6-9 or 10-23) and the days from COVID-19 onset to response (41-110, 111-127 or 128-193).

	N	Incidence rate ratio	95% CI	P value
No. of 21 comorbidites				
0†	218	1		
1	122	1.52	1.02 to 2.25	0.038
≥2	94	2.52	1.58 to 4.02	<0.001
No. of 23 COVID-19 symptoms				
0–5†	99	1		
6–9	167	1.97	1.20 to 3.23	0.007
10–23	168	4.16	2.57 to 6.72	<0.001
Body mass index, kg/m^2	434	0.99	0.97 to 1.02	0.63
Time from onset of symptoms, days				
41–110	143	1.27	0.86 to 1.87	0.24
111–127	152	1.26	0.85 to 1.86	0.25
128–193*	139	1		

Figure 4. Multivariable negative binomial regression analysis of the data from 434 participants. Showing the determinants of the number of COVID-19 related symptoms at follow-up (Stavem et al., 2021).

The majority of the responding people, 133 men (67 percent) and 133 women (53 percent), reported no COVID-19 related symptoms at the time of the survey. Also, the median amount of symptoms decreased significantly and went from 8 (6-11) during the acute COVID-19 phase to a median of 0 (0-2). The amount of symptoms at follow-up is associated with the number of comorbidities and the symptoms present during acute COVID-19, whilst no other independent variable was associated with the amount of symptoms at follow-up. Figure 4 shows the incidence rate ratio for the variables; number of comorbidities, number of COVID-19 symptoms at the acute phase and the time from the onset of symptoms to the day of the follow-up. The incidence rate ratio significantly increases in people with 1 and 2 or more comorbidities, suggesting that people with comorbidities have a higher chance of developing persistent symptoms related to COVID-19. This is the same for people with 6 to 9 symptoms during acute COVID-19 and especially for people with 10 to 23 symptoms. The time from the day of onset of symptoms to the day of follow-up shows to be less significantly related to the amount of persistent COVID-19 related symptoms.

2.3 Treatment of hospitalized individuals

Acute respiratory distress syndrome (ARDS) is defined by the Berlin criteria, which is divided into three exclusive categories of ARDS. The categories are based on the degree of hypoxemia, either mild, moderate or severe, and four other variables; radiographic severity, positive end-expiratory pressure, respiratory system compliance and corrected expired volume per minute (ARDS Definition Task Force et al., 2012).

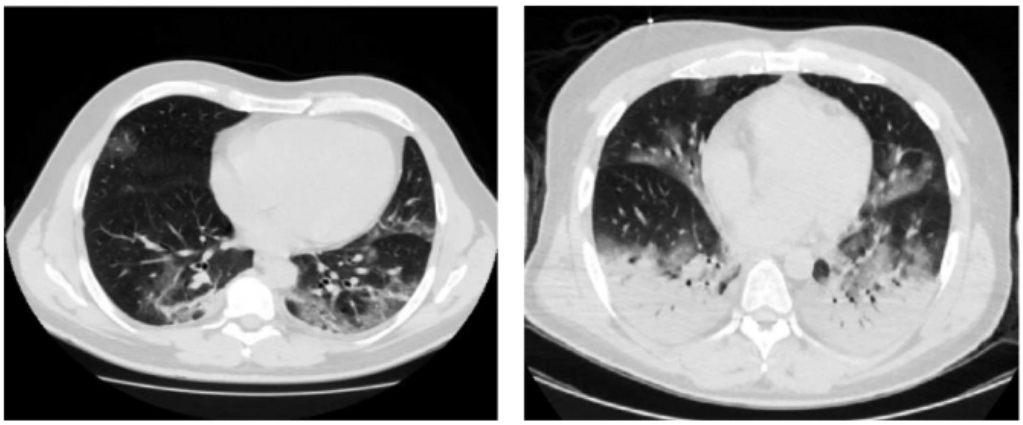

Figure 5. CT scans of the lungs of two patients with COVID-19 pneumonia that meet the requirements for ARDS Berlin definition. They recorded the following variable; Left: lung weight of 1192 gram, gas volume of 2774 milliliter, 8.4 percent of non-aerated tissue and pulmonary compliance of 80ml/cmH_2O. Right: lung weight of 1441 gram, gas volume of 1640 milliliter, 39 percent of non-aerated tissue and pulmonary compliance of 43ml/cmH_2O (Gattinoni, Chiumello, et al., 2020).

COVID-19 pneumonia can meet the conditions required for ARDS, but can present as an atypical form of ARDS. A dissociation between the severity of hypoxemia and the relatively well maintained respiratory mechanics is observed. Lung gas volume was well preserved in a group of COVID-19 patients, which is in contrast what is expected from severe ARDS. This is seen in figure 5, where the lungs of the patient on the left show a well preserved lung gas volume (2774 ml) with a low percentage of non-aerated tissue and a high pulmonary compliance, indicating the atypical form of ARDS. The lungs of the patients on the right show a decreased lung gas volume (1640 ml) with a higher percentage of non-aerated tissue and a low pulmonary compliance, indicating for severe ARDS (Gattinoni, Chiumello, et al., 2020). The severe hypoxemia occurring in lungs with well-preserved lung gas volume is possibly explained by the vascular dysfunction and impaired pulmonary blood flow seen in COVID-19 patients (Menter et al., 2020). High positive end-expiratory pressure and prone positioning are commonly used to treat severe ARDS, however the question remains whether this is the right treatment for people with poorly recruitable lungs, as seen in COVID-19 patients (Pan et al., 2020). High positive end-expiratory pressure could result in hemodynamic impairment and fluid retention in poorly recruitable lungs. Intubation should be prioritized in patients that show excessive inspiratory efforts during non-invasive ventilation or continuous positive airway pressure to avoid

self-inflicted pulmonary damage (Brochard et al., 2017; Gattinoni, Coppola, et al., 2020). The self-inflicted damage on top of the damage caused by COVID-19 could lead to a worse outcome for patients and even longer medical rehabilitation. They suggest that maintaining the lowest possible positive end-expiratory pressure and gentle ventilation is able to give patients more time to recover from the SARS-CoV-2 infection, whilst preventing any additional damage caused to the lungs.

Discussion

A high percentage of hospitalized COVID-19 patients have comorbidities like hypertension. Chronic obstructive pulmonary disease, diabetes and coronary heart disease (Chen et al., 2020; Zhou et al., 2020). This became clear in the early stages of the pandemic, however it was not understood why. Pinto et al., 2020 used lung transcriptome data from other studies collected from the Gene Expression Omnibus (GEO). The lung transcriptome data was used to investigate differentially expressed genes in lung samples from people with morbidities like chronic obstructive pulmonary disease and pulmonary arterial hypertension compared to healthy individuals. They found that ACE2 expression was increased in people with morbidities. This was associated with a higher chance of developing a more severe form of COVID-19, as ACE2 is the crucial receptor for SARS-CoV-2 host cell binding and entry. This is supported by the fact that more severe cases of COVID-19 patients showed a significantly higher viral load in nasopharyngeal swab samples than those experiencing a mild case of COVID-19 (Liu et al., 2020).

The lung transcriptome data used from the Gene Expression Omnibus by Pinto et al., 2020 did not include data from studies from COVID-19 patients. So they do not show whether ACE2 was expressed in these COVID-19 patients with comorbidities. Also, the mechanism behind the upregulation of ACE2 in patients with severe comorbidities is not addressed. It does, however, shed light on the possible explanation for the higher chance of severe COVID-19 in patients with comorbidities, the upregulation of the crucial ACE2 receptor.

The amount of comorbidities during COVID-19 was not only linked to a more severe acute phase of COVID-19, but also to an increase of persistent symptoms after recovering from COVID-19. 451 people in Norway that were previously, between 1,5 and 6 months ago, tested positive for SARS-CoV-2 answered a survey set up by Stavem et al., 2021. The respondents were not hospitalized and asked about their symptoms during the acute phase of COVID-19, symptoms after COVID-19 and the amount of comorbidities experienced together with COVID-19. The analysed data showed that the amount of symptoms and comorbidities experienced during acute COVID-19 are associated with the amount of COVID-19 related symptoms at the time of the survey. However, the number of days from the onset of COVID-19 symptoms to the day of follow-up show not to be significantly related to the amount of persistent COVID-19 symptoms. Further studies need to provide more details about the length of persistent symptoms.

Persistent symptoms are not only common for COVID-19, as many viral and bacterial infections show lasting symptoms (Metlay et al., 1997). However, the persistent COVID-19 related symptoms can be studied more in depth, as more than 175 million people are infected all over the world and possibly helping studies that investigate persistent symptoms from other viral and bacterial infections. The survey did not assess the severity of the symptoms and fatigue in the respondents, a symptom seen frequently in recovered COVID-19 patients (Carfì et al., 2020), limiting this study. There is also a chance that the responses in their study are subjected to bias as only 48% of the invited 938 people responded to the questionnaire. People with a very mild

COVID-19 might not be interested enough to participate in the survey, resulting in a bias in the data collected from the survey.

Furthermore, the way severe COVID-19 patients are treated in the hospital could improve their medical rehabilitation and decrease the amount of persistent COVID-19 related symptoms. The pneumonie seen in COVID-19 can meet the conditions that are required for acute respiratory distress syndrome (ARDS). Severe ARDS is often treated with high pressure end-expiratory pressure and prone positioning. It is questionable whether this treatment is beneficial for COVID-19 patients. COVID-19 patients present an atypical form of ARDS, with lungs that are poorly recruitable (Gattinoni, Coppola, et al., 2020; Pan et al., 2020). High positive end-expiratory pressure could lead to more self-inflicted pulmonary damage in the form of hemodynamic impairment and fluid retention (Brochard et al., 2017). Gattinoni, Coppola, et al., 2020 therefore suggest that an as low possible positive end-expiratory pressure and gentle ventilation is applied to these patients to minimize the damage caused by the ventilation. It is difficult to find one optimal treatment for COVID-19 pneumonia, as the damage to the lungs may vary from person to person. Therefore, it is important that the pulmonary damage seen in COVID-19 pneumonia is further investigated to create the best treatment.

The immune system also plays a big role in lung injury. Resident and recruited macrophages of the lungs play a role in the initiation, development and resolution of ARDS (Matthay et al., 2019). Also, cytokine dysregulation is seen as a role playing factor in COVID-19 immunopathology by most data (McGonagle et al., 2020). Together with other mechanisms of the immune system, they play an important role in the outcome of the pulmonary damage in COVID-19. This should be taken into account, as I was unable to include this in this literature research, as the subject of the literature research would become too broad and unclear.

The importance of fully understanding the mechanisms behind the spread and pathology of SARS-CoV-2 is becoming more apparent the longer the pandemic pursues. The pandemic has negatively influenced the social and economic situation in almost all countries in the world and public healthcare is unable to perform its everyday medical procedures. Most healthcare facilities showed not to be able to react to the surge in demand caused by this pandemic (Hick et al., 2020). The surge in demand, together with the backlog of everyday public healthcare, the delay of medical operation and more people with undiscovered illnesses will increase the burden on healthcare systems even further. The importance in fully understanding these types of pandemics is in the fact that healthcare systems will be more prepared to battle them. This is not the first epidemic caused by a coronavirus, as both the epidemic in 2002-2003 of severe acute respiratory syndrome (SARS) and in 2012 of Middle East respiratory syndrome (MERS) were caused by the single-stranded RNA virus (Drosten et al., 2003; Zaki et al., 2012). And it is feared that this will not be the last outbreak of a zoonotic virus, as the human population keeps increasing and humans are coming closer to the living environment of wild animals (Meslin, 1995). We are still fighting the current pandemic with no clear end in sight, it is still unsure whether we are even able to fully fight off SARS-CoV-2. Recombination of the genome of

SARS-CoV-2 leads to more variants that are possibly more contagious or lethal, or even unaffected by the created vaccines. It is therefore important to identify the group in the population that is most vulnerable to SARS-CoV-2 and has a higher chance of developing severe COVID-19. Protecting this group of people with morbities, by vaccination and correct treatment, helps to reduce the amount of people with severe COVID-19 and decreases the death toll of SARS-CoV-2. Finally, decreasing the social and economic damage caused by the pandemic, as well as being more prepared for possible future pandemics.

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